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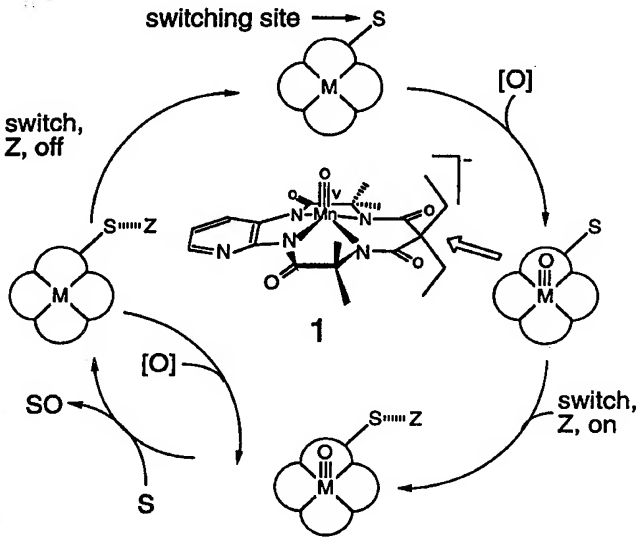
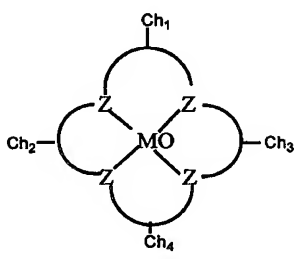
(54) Title: HOMOGENEOUS OXIDATION CATALYSIS USING METAL COMPLEXES

(57) Abstract

The present method provides a method of transferring oxygen to at least one oxidizable site on a target compound. The method includes the steps of selectively oxidizing an oxidizable site on a target compound by reacting in solution: the target compound, a source of oxygen atoms, a source of a Lewis acid, such as a proton, alkali, alkaline earth, rare earth, transition metal or main group metal ion, and a catalyst. The catalyst has general structure (I) wherein Z is preferably N, but may include O and MO is a transition metal–oxo species. The Lewis acid binds to a bidentate secondary site on the Ch_1 substituent to form a Lewis acid–catalyst complex.





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TITLE

HOMOGENEOUS OXIDATION CATALYSIS USING METAL COMPLEXES

CROSS REFERENCE TO RELATED APPLICATION

Not Applicable

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This work was supported by a grant from the National Institutes of Health. (5RO1GM55836). The U.S. Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

The present invention relates to the field of oxidation catalysts and catalysis. More particularly, the invention relates to the field of catalysts useful for the oxidation of olefins, in particular, the enantioselective oxidation of olefins.

Selectivity in reactions, including chemoselectivity, regioselectivity, and stereoselectivity, is of paramount significance both in chemistry and in biology. Selection in reactions among or between different functional groups, such as alcohols, ketones, aldehydes, carboxylic acids and others is referred to as chemoselectivity. Regioselectivity refers to the selection of one orientation, or regioisomer, over any other that could be created or destroyed in a substrate altered by the reaction. Stereoselectivity encompasses the concepts of diastereoselectivity (selection among diastereomers, two chemicals that have the same connectivity that are nonsuperimposable nonmirror images) and enantioselectivity (selection between two possible entantiomers, two chemicals that have the same connectivity that are nonsuperimposable mirror images). For example, in the production of various pharmaceuticals, it has been learned, often with disastrous consequences, that one enantiomer has beneficial properties while the other enantiomer is harmful. To

attain the desired degree and type of selectivity, chemists employ an array of reagents that incorporate almost the entire periodic table; elements are collected from every accessible environment. Methods of using chiral transition metal catalysts for enantioselectively epoxidizing a prochiral olefin and enantioselectively oxidizing a prochiral sulfide are disclosed in Jacobsen et al., U.S. Patent No. 5,637,739.

In contrast, Nature uses the relatively small number of elements available in each local environment and uses these within the limitations of solvent availability and temperature accessibility to practice the elaborate chemistry of life. Nature succeeds with its selectivity objectives by accomplishing a reagent design and a systems interconnectedness that appear boundless in sophistication; and through this design complexity, Nature is able to use a small group of elements in a much wider range of structural and functional roles than chemists have achieved for the same. In this strategic difference lies a root cause of much of the environmental damage attributable to chemistry, certainly to technological chemistry practiced without appropriate understanding or due care. By employing a diversity of elements to attain selectivity, chemists are able to function within a comparatively simplistic design constellation. In the process, living things are confronted with elements that are unfamiliar and, consequently, often toxic. The preferred reagents that expand the range of reactivity of low toxicity trransition elements, e.g. manganese and iron, can lead to processes that are environmentally more desirable than currently exist.

Efforts toward the design of oxidatively robust chelating ligands to support peroxide-activating catalysts of manganese and iron have been reported in T. J. Collins, *Accounts of Chemical Research* 27, 279-285 (1994); and in F. C. Anson, et al., *J. Am. Chem. Soc.* 106, 4460-4472 (1984). A particularly robust tetradentate ligand is disclosed in co-pending United States Patent Application, Serial No. 08/681,237 of T. Collins et al. for "Long-Lived Homogenous Oxidation Catalysts", which is hereby incorporated herein by reference. The development of the first stable manganyls, i.e., Mn^{V}-oxo complexes, were reported in T. J. Collins, S. W. Gordon-Wylie, *J. Am. Chem. Soc.* 111, 4511-13 (1989) and in T. J. Collins, R. D.

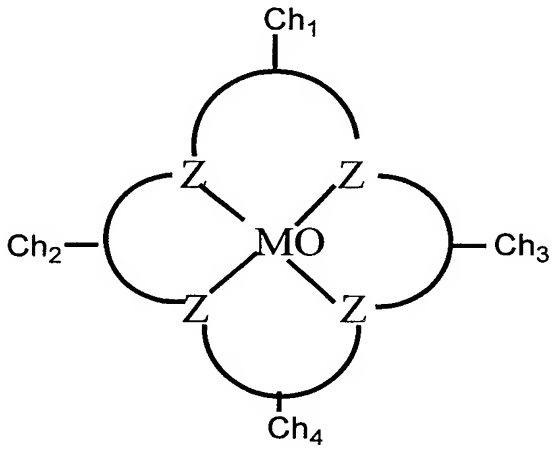
Powell, C. Slebodnick, E. S. Uffelman, *J. Am. Chem. Soc.* 112, 899-901 (1990); the complex described in the latter article is also stable in aqueous environments. While the macrocyclic tetraamide ligands described in the aforementioned 1989 and 1990 Collins et al. *J. Am. Chem. Society* articles are stable when coordinated to oxidizing metal ions, these ligand-metal complexes and their analogues are not highly reactive oxygen atom transfer agents. This contrasts with systems employing dianionic porphyrin and salen tetradentate ligands, where Mn^{V} and Mn^{IV}-oxo complexes are the purported reactive intermediates in a variety of O-atom transfer processes. *See*, E. Srinivasan, P. Michaud, J. K. Kochi, *J. Am. Chem. Soc.* 108, 2309-2320 (1986); J. T. Groves, M. K. Stern, *J. Am. Chem. Soc.* 110, 8628-8638 (1988); W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* 112, 2801-2803 (1990).

BRIEF SUMMARY OF THE INVENTION

It is believed that the muted reactivity of the prior tetraamide Mn^{V} -oxo complexes results from the higher negative charge and σ-donor capacities of the tetraamide ligands vis-a-vis the porphyrin or salen ligands. The present invention uses a new oxidatively and hydrolytically robust transition metal complex, containing metals such as iron or manganese, where in its active form the oxo ligand species is reactive in O-atom transfer reactions to organic nucleophiles. Significantly, the system of the present invention also employs a second reaction to increase the electrophilicity of the oxo ligand. Attachment of Lewis acidic species usually in the form of positively-charged ions in the immediate vicinity of the metal-oxo moiety of a modified tetradentate ligand delivers the targeted increase in O-electrophilicity and thereby results in effective metallo O-atom transfer agents, as shown schematically in Figure 1 for one embodiment of the catalyst.

The present invention provides a method of transferring oxygen to at least one oxidizable site in a target compound having a plurality of oxidizable sites or of transferring oxygen to an oxidizable site of a prochiral species. Oxidizable, as used herein, refers to any site that will accept an oxygen atom, such as, an olefin or an

alkynyl site, or that is subject to another form of oxidation produced by the oxidizing catalyst systems presented hereine. The case of compounds with a plurality of oxidizable sites will be explained in detail. Oxidation of prochiral species to produce chiral compounds proceeds similarly except that only one oxidizable site need be present and the catalyst system must be one that possesses' chirality. The method comprises adding to a solution containing a target compound having a plurality of oxidizable sites therein, a source of oxygen atoms, a source of a Lewis acid species, most commonly a cationic species, and, a catalyst having the structure



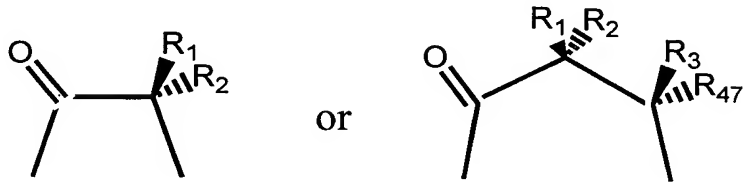
or wherein:

Z is N or O and at least one and preferably four Zs are N species;

MO is a transition metal -oxo species ;

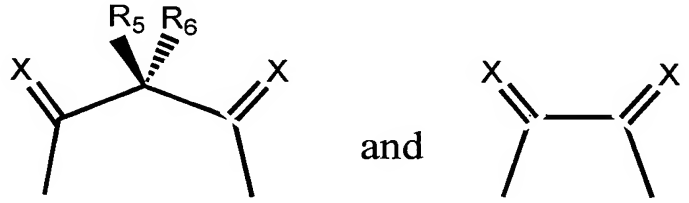
Ch_1 is selected from the group consisting of pyridine, pyrimidine, pyrazine, dicyano-pyrazine, mono- or di-, tri- or tetra- substituted benzene, benzimidazole, benzoquinone, di-imino-substituted benzene, indole, substituted crown derivatives, cryptand ligands, EDTA derivatives, five membered rings and five membered ring derivatives, porphyrin derivatives, metallated pthalocyanine based systems, bipyridyl-based systems, phenanthroline based systems and salen based systems;

Ch_2 and Ch_3 each represent a unit joining the adjacent Z atoms comprised of



wherein R_1, R_2, R_3, and R_4, pairwise and cumulatively, are the same or different and each is selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halogen, fluoroalkyl, perfluoroalkyl, fluoroalkenyl, perfluoroalkenyl, CH_2CF_3 and CF_3, or R_1, R_2, R_3 and R_4 together form a substituted or an unsubstituted benzene ring, or the paired R substituents of the R_1, R_2 or the R_3, R_4 pairs together form a cycloalkyl or a cycloalkenyl ring; and,

Ch_4 is a unit joining the adjacent Z atoms selected from the group consisting of



wherein R_5, R_6, are the same or different linked or nonlinked and are each comprised of hydrogen, ketones, aldehydes, carboxylic acids, esters, ethers, amines, imines, amides, nitro, sulphonyls, sulfates, phosphoryls, phosphates, silyl, siloxanes, alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halo, CH_2CF_3 or CF_3 , or the paired R substituents of the R_5, R_6 pair together form a cycloalkyl or a cycloalkenyl ring;

and allowing the oxidation reaction to proceed for a period of time sufficient to oxidize the desired oxidizable site in the target compound.

Those skilled in the art will recognize that Lewis acids include cationic, neutral and anionic species. The use of the term cation-catalyst

complex as used herein is intended to encompass the use of all such species as the entity that binds to the catalyst and changes its activity and is not limited to cations.

The metal ions are any Lewis acid species, such as protons, alkali, alkaline earth, rare earth, transition metal or main group metal ions.

In a preferred method for using the catalyst described above, the plurality of oxidizable sites in the target compound differ from each other in relative reactivity and the cation added to the solution is selected to selectively activate the catalyst to oxidize one oxidizable site of the target compound. The method of the invention therefore includes the steps of identifying a series of oxidizable sites on the target compound, each oxidizable site in the series having sequential reactivities ranging sequentially from a beginning oxidizable site having the highest relative reactivity of the series of oxidizable sites to an ending oxidizable site having the lowest relative reactivity of the oxidizable sites in the series of sites, adding to the solution a first cation for activating the catalyst to form a first cation-catalyst complex having a first reactivity level sufficient to oxidize a desired first oxidizable site, such that a second oxidizable site in the series of oxidizable sites then has the highest relative reactivity of the oxidizable sites remaining in the series of sites of the target compound. Following the oxidation of each available beginning oxidizable site, the first cation is optionally removed from the solution. Thereafter, a second cation for activating the catalyst to form a second cation-catalyst complex is added to the solution, the second cation-catalyst complex having a reactivity level sufficient to oxidize the second oxidizable site on the target compound, and the oxidation reaction proceeds for a period of time sufficient to permit the oxidation of each second oxidizable site on the target compound such that the next oxidizable site in the series of oxidizable sites on the target compound has the highest relative reactivity of the oxidizable sites remaining in the series of sites. Following the oxidation, the second cation is

optionally removed from the solution. The foregoing steps are repeated by adding cations to the solution, allowing the oxidation to proceed and optionally removing the cation from the solution, each successive cation added to the solution forming a cation-catalyst complex having a progressively higher reactivity to effect the sequential oxidation of the oxidizable sites in the series of oxidizable sites until each ending oxidizable site is oxidized. Where the cations form strong bonds with the secondary site or sites of the catalyst, removal of the cation and the cation-catalyst complex will not be required. In addition, if removal of the cation is not necessary to permit subsequent added cations to activate the catalyst, cation removal will not be necessary.

The method may further include the enantioselective oxidation of at least one prochiral oxidizable site on a target compound such targeted compounds may have only one oxidizable site. The catalyst or cation-catalyst complex used in the enantioselective oxidation includes substituents for making the complex asymmetric such that when reacting with the prochiral oxidizable site of the target compound, the cation-catalyst complex favors the formation of one enantiomer over the other or in cases where the substrate already possesses chirality favors a selection among diastereomeric alternatives. The method may alternatively function in kinetic resolution applications in which one enantiomer of a pair in a mixture is selectively winnowed from that mixture.g23

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention can be better understood by reference to the figures which include the titles "compound 1" and $[LMn^{V} \equiv O]^{-}$as interchangeable terms for the preferred embodiment of Figure 1.

FIG. 1 is a schematic representation of the catalytic cycle that the switched oxidations of the present invention are believed to follow.

FIG. 2 is a molecular structure of the compound 1: an ORTEP drawing with nonhydrogen atoms drawn to encompass 50% of electron density wherein the Mn atom lies 0.579Å above the plane towards the oxo atom, and the coordinated oxygen is positioned symmetrically above the manganese. Selected bond lengths [Å]: Mn-O(1), 1.549(3); Mn - N(1), 1.884(4); Mn - N(2), 1.873(3); Mn - N(3), 1.881(3); Mn - N(4), 1.885(3).

FIGS. 3A and 3B illustrate, in A) the UV/Vis spectra of compound **1** (9.71 x 10^{-5} M, 3 mL sample size) wherein aliquots of $Li(OSO_2CF_3)$ in acetonitrile were added (0.06 μmol in 2 μL in initial additions); and in B) the mole ratio plot corrected for dilution.

FIG. 4 represents the infrared spectra (polyethylene film) of compound **1** (light line) and of lithiated compound **1** (heavy line) showing the 15 cm^{-1} increase in the $\nu(Mn\equiv{}^{18}O)$ band associated with lithiation of the switching site. The Li^+ binding induces a substantial drop in donor capacity of the macrocyclic tetraamido-N ligand, a drop that is compensated for by an increase in the binding energy of the oxo ligand.

FIGS. 5A and 5B represent, in A) rates of change of the UV/Vis absorption of compound **1** at 396 nm in the presence of triphenylphosphine and different switching ions. Normalized observed rate constants: experiment number, number of equiv of cation, cation, relative rate ± standard deviation of minimum of three runs: **1**, no cation, 0, 1; 2a, 5, Na^+, 2.7 ± 0.1; 3a, 5, Ba^{2+}, 4.8 ± 0.5; 3b, 60, Ba^{2+}, 5.7 ± 0.1; 4a, 5, Mg^{2+}, 7.0 ± 0.4; 4b, 60, Mg^{2+}, 7.2 ± 0.8; 5a, 5, Li^+, 13.5 ± 2.0; 6a, 5, Zn^{2+}, 24.5 ± 1; 6b, 60, Zn^{2+}, 24.1 ± 0.8; 5b, 60 Li^+, 25.0 ± 0.5; 2b, 60, Na^+, 506.4 ± 7.0; 7a, 5, Sc^{3+}, 1246.0 ± 206.1; 7b, 60, Sc^{3+}, 1577.6 ± 290.0; and in B) the expansion of the time scale showing the fastest oxidations.

FIG. 6 schematically illustrates the ligand synthesis.

FIG. 7 schematically illustrates the metal insertion, for manganese.

FIG. 8 is the ^{1}HNMR spectrum of the species, $[LMn^V\equiv O]^-$. The low symmetry resulting from the presence of the pyridine-N and the Mn(O) is reflected in the observation of four methyl resonances, cc'dd'.

FIGS. 9A and B illustrate the UV/Vis study of Na^+ binding to $[LMn^V{\equiv}O]^-$ for various molar equivalents of Na^+, 0.0 (shown by the longer dashed line, ----), 25 (shown by the shorter dashed line, ---), and 60 (shown by the darkest solid line). The mole ratio plot indicates that there are two binding processes. One is Na^+ binding into the switching site and the other binding event is believed to occur at one of the amide oxygens.

FIGS. 10A, B, C and D illustrate the UV/Vis and IR study of Zn^{2+} binding to $[LMn^V{\equiv}O]^-$ for various molar equivalents of Zn^{2+}, 0.0 (shown by the longer dashed line, -- -- --), 0.23 (shown by the shorter dashed lines, - - -) and 0.69 (shown by the darkest solid line).

FIGS. 11A, B, C and D illustrate the UV/Vis study of Mg^{2+} binding to $[LMn^V{\equiv}O]^-$ for various molar equivalents of Mg^{2+} with 0.0 being shown by longer dashed lines, 0.30 shown by shorter dashed lines and 1.06 shown by the darkest solid line.

FIGS. 12A and B illustrate the UV/Vis study of Ca^{2+} binding to $[LMn^V{\equiv}O]^-$ for various molar equivalents of Ca^{2+}.

FIGS. 13A and B illustrate the UV/Vis study of Ba^{2+} binding to $[LMn^V{\equiv}O]^-$ for various molar equivalents of Ba^{2+}.

FIGS. 14A and B illustrate the UV/Vis study of Sc^{3+} binding to $[LMn^V{\equiv}O]^-$ for various molar equivalents of Sc^{3+}. The Sc^{3+} exhibits complex binding behavior, however, only one equivalent is required to reach the endpoint.

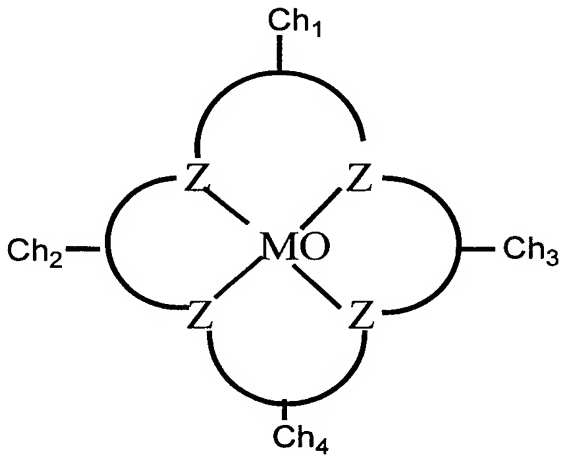
FIGS. 15A-F illustrate the O - atom reactivity studies of $[LMn^V{\equiv}O]^-$ and tetramethylethylene monitored by ^{13}C-NMR; growth on the resonances of the carbon product over time are shown in a progression from light to dark traces.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiment of the catalyst used in the method of the present invention contributes to the "greening" of chemistry by invoking the principle that reagents should be composed of low toxicity elements. Among the green design elements considered to be important are the following. Preferably, the metal is one

of the low toxicity elements, i.e., iron or manganese. The supporting ligand system is preferably comprised of carbon, hydrogen, nitrogen, oxygen and other biologically common elements. It is preferred that the primary oxidant is one found widely in Nature, such as oxygen or one of its reduced derivatives, especially hydrogen peroxide. This reasoning constitutes a significant environmental case for advancing ligand design to afford nontoxic, long-lived iron and manganese catalysts for activating peroxides and oxygen for a wide range of homogeneous oxidations.

The catalysts found to be useful for the methods of the present invention have the general structure:



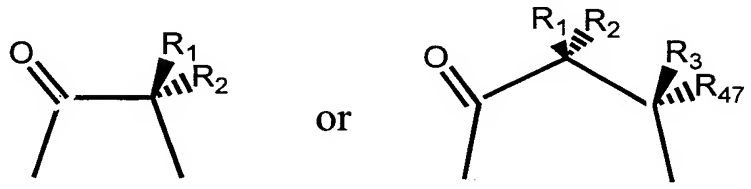
wherein:

Z is N or O and at least one Z, and preferably four Zs are N;

MO is a transition metal -oxo species ;

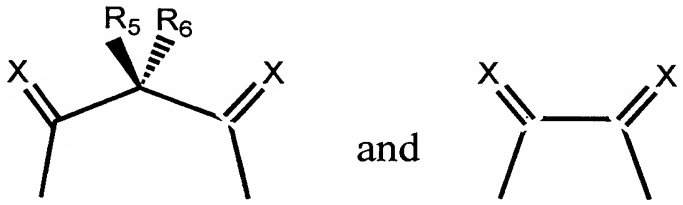
Ch_1 is selected from the group consisting of pyridine, pyrimidine, pyrazine, dicyano-pyrazine, mono- di- tri- or tetra- substituted benzene, benzimidazole, benzoquinone, dimino-substituted benzene, indole, substituted crown derivatives, cryptand ligands, EDTA derivatives, five membered rings and five membered ring derivatives, porphyrin derivatives, metallated pthalocyanine based systems, bipyridyl-based-systems, phenanthroline based systems and salen based systems, in accordance with the representations for such substituents as set forth in Table I herein ;

Ch_2 and Ch_3 each represent a unit joining the adjacent Z atoms comprised of



wherein R_1, R_2, R_3, and R_4, pairwise and cumulatively, are the same or different and each is selected from the group consisting of alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halogen, CH_2CF_3 and CF_3, or R_1, R_2, R_3 and R_4 together form a substituted or an unsubstituted benzene ring, or the paired R substituents of the R_1, R_2 or the R_3, R_4 pairs together form a cycloalkyl or a cycloalkenyl ring; and,

Ch_4 is a unit joining the adjacent Z atoms selected from the group consisting of



wherein R_5, and R_6, are the same or different, linked or nonlinked, and each is comprised of hydrogen, ketones, aldehydes, carboxylic acids, esters, ethers, amines, imines, amides, nitro, sulphonyls, sulfates, phosphoryls, phosphates, silyl, siloxanes, alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halo, CH_2CF_3 or CF_3 , or the paired R substituents of the R_5, R_6 pair together form a cycloalkyl or a cycloalkenyl ring.

A preferred embodiment of the catalyst is the tetraamido ligand shown in Figure 1, referred to herein as compound **1**. The catalyst used in the method of the invention contains a bidentate secondary site which in compound **1** is comprised of the pyridine nitrogen and the adjacent amide oxygen. The electronic influence of binding a secondary ion is transmitted to the Mn(O) moiety via a combination of σ

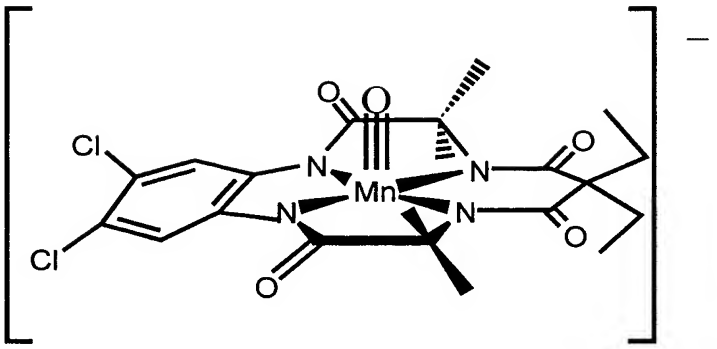
and π perturbations. Such a binding increases the electrophilicity of the oxo ligand, thereby increasing its O-atom transfer reactivity. The secondary binding is referred to herein as a 'switching' event, an event whereby a secondary reaction is arranged in time to cause a primary reaction to proceed to deliver a targeted reactivity and selectivity at an acceptable rate.

In the method of the present invention, switching processes are used to activate compound **1** such that it performs useful oxidations on convenient time scales. By manipulating the Lewis acid or cation that binds to the secondary site, the relative reactivity of the catalyst can be controlled. Using this technique, as explained in more detail below, the chemo- and regio-selectivity and sequence of oxidation reactions at desired sites in a larger compound having a plurality of possible oxidation sites can be controlled. In addition, the introduction of chirality at desired prochiral sites can be controlled, by synthetically modifying the environment surrounding the active site of the catalyst to introduce asymmetry or by bringing asymmetry to the cation catalyst complex via groups attached to the switching cation. The size and shape of the complex can be altered to have it favor contact with one side of the desired oxidation site, for example, an olefin, in preference to the other side.

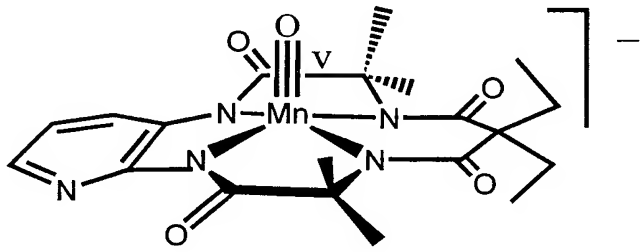
A cationic ligand(L)-metal(M)-oxo(O)-species $\{[LM=O]^+\}$ has been used as the active oxidant in metal catalyzed olefin oxidations similar to those of the present invention, generally as follows:

$[LM]^+ + [O] \rightarrow \{[LM=O]^+\} +$ olefin $\rightarrow [LM]^+ +$ epoxide (or other oxidation product)

The macrocyclic tetraamides



give stable anionic $[LM \equiv O]^-$ species, such as $[LMn^V \equiv O]^-$. These anionic manganyl species are not very active as O-atom transfer agents. Alteration of the anionic species to provide neutral or cationic species was found to enhance the catalyzing ability of the manganese species in oxidation reactions. In one method of the present invention, a bidentate secondary ion binding site was added to the macrocycle



to permit tuning of the charge, modification of the donor capacity of the amides and alteration the kinetics and thermodynamics of the axial ligand binding to the metal. The $[LMn^V \equiv O]^-$ complex was titrated with triflate-$[SO_3CF_3]$ salts of representative alkali, alkaline earth, or transition metal cations. The changes were followed by UV/Vis spectroscopy. Mole ratio plots were generated and interpreted for understanding of the binding process. An example is shown in Fig. 3 using Li^+ as the cation where $K=9.0 \times 10^4 - 1.2 \times 10^5$ and $pK=4.95 - 5.08$. The mole ratio plot indicates that there is only one binding process.

The changes in the Mn^V band in the UV/Vis spectrum were also monitored for Na^+, Zn^{2+}, Mg^{2+}, Ca^{2+}, Ba^{2+} and Sc^{3+}. *See,* Figs. 9-14. Cation-catalyst complexes having transition metal ions Ru and Rh have been prepared and have successfully catalyzed oxidations.

As shown in Fig. 5, in an initial test reaction, the $[LMn^{V}\equiv O]^{-}$ switching complex was reacted with PPh_3 to produce $Ph_3P=O$ in the absence and in the presence of the switching ions. The decay of the Mn^{V} band in the UV/Vis spectrum was monitored.

The results demonstrate that the presence of switching ions dramatically enhances the O-atom transfer reactivity. The rate can be controlled by the choice of the secondary ion. The successful catalytic O-atom transfer to tetramethylethylene (*see* Fig. 15) together with the ability to control the rate of the reaction by selective manipulation of the secondary ion demonstrates that the oxidation catalysts of the present invention are useful in the oxidation of a variety of substrates, including olefins.

Referring to Fig. 15, for example, the selective oxidation method of the present invention may proceed as follows: the oxo catalyst $[LMn^{V}\equiv O]^{-}$ and a source of the desired alkaline, alkaline earth or transition metal cation, main group metalion and a source of oxygen atoms, such as a peroxy compound or oxidant, are mixed at room temperature in a solution containing a solvent and a target compound having a plurality of olefin sites. If necessary to produce a reaction at an acceptable rate, the solution is heated. The reaction produces an oxidation at the most reactive olefin site or sites and any others that the reactivity of the cation-catalyst complex will accommodate.

$[LMn^{V}\equiv O]^{-}$ + switches or cations + olefin or target compound + [O] → oxidized product or an epoxide at one or more selected sites of the olefin

A specific reaction is shown in Fig. 15.

To control the oxidation so that only one site, or only sites having a certain reactivity are oxidized, the first cation used is one that yields the cation-catalyst complex of the lowest reactivity. The low-reactivity cation-catalyst complex produced upon binding with the cation will oxidize only the most reactive olefin sites on the substrate, or target compound. In this manner, a series of olefin sites from the most reactive to the least reactive can be oxidized respectively, by catalysis beginning with the cation bound to the secondary binding site of the oxo-tetraamido

ligand that yields the least reactive cation-catalyst complex, $[LM(O)]^+$ and proceeding to the most reactive cation-catalyst complex. A typical sequence for a target compound having a plurality of olefin sites, a, b, c, d, e, f, g, etc., is to add a source of a first cation, one yielding the least reactive cation-catalyst complex, to the reaction mixture described above. The cation will bind to the secondary binding site of the oxo catalyst. The cation-catalyst complex will initiate the oxidation of the most reactive olefin site, the first olefin site a, on the target compound. The reaction will stop and the first cation optionally will be removed, if necessary. A source of a second cation will be added to the reaction mixture and will bind to the secondary binding site of the oxo catalyst which will in turn initiate the oxidation of the most reactive remaining olefin site , a second olefin site b, on the target compound, (the most reactive site originally present having been previously oxidized). Then the second cation will be removed, if necessary from the reaction mixture and a third cation will be added to bind to the secondary binding site of the oxo-catalyst whereupon the catalyst will initiate the oxidation of the most reactive remaining olefin site, a third olefin site c, on the target compound. The process can continue to effect the sequential oxidation of different olefin sites, d, e, f, g, etc., on the target compound. Sequential reactivity can also be obtained with one cation whereby the temperature is the controlling factor. Thus, the cation/catalyst complex oxidizes the least reactive site at a temperature chosen so that only this site reacts. On raising the temperature, a temperature can be found where the two mostt reactive sites react selectively compared to the others, etc. The foregoing is an example of chemoselectivity. In a compound where olefins are not identical, or where there are groupings of olefins that are identical and groupings of olefins that are not identical in the same compound, one of the olefins or one grouping of olefins will be more reactive than the other olefins or groups of olefins. Each olefin or olefin group will differ somewhat in reactivity. Because the reactivities of the various functional groups adjacent to or attached to the double bond of the olefin sites will be known, selection of oxidation at one functional group in preference to oxidation at another functional group can be controlled. The reactivity of the oxo-catalyst can also be

controlled by changing the metal ion, M, to another transition metal. Iron, for example, is vastly more reactive than manganese in these catalyst systems. Manganese is preferred for systems where a mild oxidation catalyst is called for.

The switching catalysts are useful for incorporating asymmetry into prochiral substrates. The enantioselectivity with regard to the prochiral sites on a target compound can be controlled by the presence of asymmetry in the cation-complex. The oxygen atom transfer site on the catalyst must be able to reach the olefin, or other oxidizable prochiral site of the target compound. Chirality can be built into the oxo-catalyst or brought to it via the switching cation and groups attached thereto. By selecting the substituents on the catalyst, the size, shape and chiral character of the catalyst can be controlled. Numerous variations for substituent groups and the manner of making them are disclosed in the Collins et al. patent application cited above and incorporated herein and in co-pending United States Patent Application, Serial No. 08/681,187 of S. Gordon-Wylie et al., for "Synthesis of Macrocyclic Tetraamido N-Ligands", the relevant portions of which are hereby incorporated herein by reference. Similarly, the size and shape of the target compound and the position of functional groups on the target compound, particularly those nearest the double bond, will control which side of the olefin double bond the catalyst can approach to effect oxygen atom transfer to the olefin, i.e., oxidation of the olefin site. Selectivity occurs where one enantiomer is created or destroyed in preference to the other enantiomer that could have been created or destroyed. While there are commercially available catalysts that can provide enantioselectivity, the best are limited to 10 to 20 cycles or turn-overs of the oxidation catalyst. It has been observed that the catalyst system of the present invention is very long-lived and appears to regenerate in the presence of a source of oxiditing power preferably oxygen or one of its reduced derivatives many, many more times than the commercially available catalysts.

The catalyst systems of the present invention can also induce chirality by transferring sulfur compounds oxygen atoms from the switching catalyst to an

organic or inorganic substrate. A prochiral phosphorous compound, for example, can be oxidized at phosphorys or sulfur so that chiral species result.

The pyridine-substituted macrocycle (Compound **1**) shown in Figure 1 can be synthesized by an adaptation of the multistep procedure for making macrocyclic tetraamides disclosed in co-pending U. S. Patent Application, Serial No. 08/681,187 of S. Gordon-Wylie et al., cited above and incorporated herein. The parent complex without the pyridine group was reported in T. J. Collins, R. D. Powell, C. Slebodnick, E. S. Uffelman, *J. Am. Chem. Soc.* 113, 8419-8425 (1991).

The synthesis of the tetradentate ligand proceeds generally as follows . In the first step, an amino carboxylic acid, preferably an α or ß amino carboxylic acid, is dissolved in a supporting solvent and heated with an activated derivative selected from the group consisting of oxalates and malonates, such as a substituted malonyl dichloride in the presence of a base, to form an intermediate. Following completion of the selective double coupling reaction, a diamide dicarboxyl-containing intermediate is isolated. In the second step, a diamine is added to the intermediate in the presence of a solvent and a coupling agent. The diamine is one providing a secondary binding site, such as those selected from the group consisting of pyridine, pyrimidine, pyrazine, dicyano-pyrazine, mono- or di- substituted benzene, benzimidazole, indole, substituted crown derivatives, cryptand ligands, EDTA derivatives, five membered rings and five membered ring derivatives, porphyrin derivatives, metallated pthalocyanine based systems, bi-pyridyl based systems, phenanthroline based systems and salen based systems, such as those diamines shown in Table I. The coupling agent is preferably a phosphorous halide compound or pivaloyl chloride. The resulting mixture is heated and the reaction is allowed to proceed for a period of time sufficient to produce the macrocyclic tetradentate compounds, usually 48-72 hours at reflux when pyridine is the solvent. Typically, stoichiometric amounts of the reactants are used.

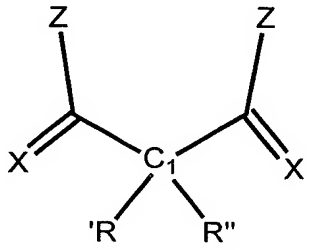
The substituent groups on the amino carboxylic acids, the activated oxalate or malonate derivatives and the diamines may all be selectively varied so that the

resulting tetradentate macrocycle can be tailored to specific desired end uses. Variation in the substituents has little or no effect on the synthesis methodology.

Once the macrocyclic ligand has been prepared, the compound is complexed with a metal ion, preferably a transition metal ion from Groups 6 (Cr, Mo, W), 7 (Mn, Tc, Re), 8 (Fe, Ru, Os), 9 (Co, Rh, Ir), 10 (Ni, Pd, Pt), and 11 (Cu, Ag, Au) of the Periodic Table of the Elements or those having oxidation states of I, II, III, IV, V, VI, VII or VIII. Because the preferred use of the catalyst systems of the present invention is environmentally sound oxidations, those metals that are nontoxic are preferred, with manganese and iron being the most preferred.

If the resulting metallated complex is then combined with a strong O-atom transfer oxidant, preferably a peroxide, such as hydrogen peroxide, t-butyl peroxide, or cumyl peroxide, a ligand metal oxo complex is formed. Any source of oxygen atoms can be used.

For particularly robust oxidation catalysts which are useful when the metal is iron, Ch_4 has the general structure



wherein:

Z is the metal complexing atom, preferably N; X is a functionality resistant to oxidation when the metal complex is in the presence of an oxidizing medium; and

R' and R" are the same or different and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly within R' and R" and with the cyclic carbon to which they are bound, are sterically hindered and are conformationally hindered such that oxidative degradation of the metal complex is restricted in the presence of an oxidizing medium.

X is preferably oxygen or NR_s, wherein R_s is methyl, phenyl, hydroxyl, oxylic, CF_3 and CH_2CF_3. R' and R" are each preferably hydrogen, methyl, halogen, CF_3, and if linked, a cycloalkyl such as cyclopentyl, cyclobutyl, cyclohexyl or cyclopropyl.

Alternatively, when in milder oxidation environments, for example when the metal is manganese, R' and R" can be any one of the groups recited for Ch_4 above or additionally those chosen for R_5 and R_6 on page 11. Oxidatively robust oxidation catalysts are described in more detail in the T. Collins et al., U.S. Patent Application, Serial No. 08/681,237 filed July 22, 1996 cited above and incorporated herein by reference.

Manganese insertion into the macrocycle of compound **1** is complicated in that both the primary tetraamide and the secondary site readily bind manganese under basic aprotic conditions. Thus, manganese must be removed from the secondary site after the insertion into the primary site. In the case of manganese, this is achieved by basic aqueous workup conditions. A useful synthesis proceeded as follows.

Example 1

The ligand (425 mg, 1.05×10^{-3} mol), was dissolved in dry tetrahydrofuran (THF, 40 mL) under an inert atmosphere, and lithium [bis(trimethylsilylamide)] (6.32 mL of 1.0M THF solution, 6.3×10^{-3} mol) was added. The mixture was stirred (5 mins) and manganic acetylacetonate, $Mn(acac)_3$ (557 mg, 1.58×10^{-3} mol), was then added as an acetonirile solution (10 mL). The reaction mixture was stirred (2 hours) and the solution was then evaporated to dryness in air on a rotary evaporator. The solid residue was dissolved in minimal amount of water and filtered to remove the solid residue. The filtrate was evaporated to dryness under reduced pressure and the resulting solid, $Li[LMn^{III}]$, was dissolved in acetone and filtered. The filtrate was treated with excess *tert*-butylhydroperoxide (TBHP) solution (0.586 mL, 5.25 x 10 mol, 90% TBHP containing 5% *tert*-butyl alcohol and 5% water). The ensuing reaction was monitored by a color change from a starting color of bright orange to a final color of deep red-brown. Excess tetraphenylphosphonium chloride (2.0 g, 5.25

x 10^{-3} mol) dissolved in water (20 mL) was added to the product solution which contained Li[LMn^{V}(O)], i.e. the lithium salt of compound **1** essentially in quantitative yield. The solvent volume of the mixture was reduced by rotary evaporation giving a suspension of [Ph_4P]compound **1** in water. Single crystals were grown by vapor diffusion of pentane into an ethyl acetate solution of [Ph_4P]compound **1** at room temperature; the results of an X-ray crystal structure determination are shown in Figure 2 for the compound 1 anion. $(C_6H_5)_4P$[compound **1**]: Anal. Calcd for $C_{44}H_{45}MnN_5O_5P$: C, 65.26; H, 5.60; N, 8.65; P, 3.82. Found C, 65.42; H, 5.67; N, 8.85; P, 3.89. ^{1}H NMR (chloroform-d_1): (*See* Fig. 8) $(C_6H_5)_4P$[compound **1**] δ 8.58 (m, 1 H), 8.10 (m, 1 H), 7.47-7.85 (m, 20 H), 6.86 (m, 1H), 2.05 (q, 2 H, J = 7.3 Hz), 1.97 (q, 2H, J = 7.3 Hz), 1.86 (s, 3 H), 1.85 (s, 3 H), 1.81 (s, 3 H), 1.80 (s, 3 H), 0.83 (t, e H, J = 7.7 Hz), 0.55 (t, 3 H, J = 7.4 Hz). ESI-MS (negative ion): m/z 470.1, [compound 1]$^{1-}$ (100%);

Crystal Data: Single crystals are orthorhombic, space group *Pbca*, with a = 14.205(2) Å, b = 19.87(2) Å, c = 28.341(4) Å, V - 7999(9) Å^3 at -100°C, and Z - 8[d_{cald} = 1.355 g cm^{-3}; μ = 4.24 cm^{-1}. A total of 7895 unique reflections ($2°<2\theta<52.16°$) were collected using ω scans with Zr-filtered Mo Kα X-radiation. The structure was solved by direct methods using SHELXS [G. M. Sheldrick, Acta Cryst., A46, (1990), 467], and refined by full-matrix least-squares on F^2 using SHELXL93 [G.M. Sheldrick, SHELXL93, *Program for Crystal Structure Refinement*, University of Göttingen, Federal Republic of Germany, 1993]. The distinction between C and N in the pyridine ring was made as follows: Since there was no difference between the heights of the peaks in the difference map, or the lengths of the bonds to each atom, both atoms were included and refined as C atoms. One of the two [that subsequently labeled N(5)] displayed more asymmetric thermal parameters on anisotropic refinement. The other [that labeled C(2)] was the only one to show a likely H atom position in a difference map. As all other hydrogen atoms could be unambiguously located in difference maps this was considered to be sufficient evidence, taken in conjunction with the temperature factor data, for making the atomic assignments. However, they are by no means certain, and these

atoms might be interchangeable. Hydrogen atoms were refined using the riding model with isotropic temperature factors set to 1.2 times that of the atom to which they were attached. Methyl hydrogens were refined as rigid groups. The crystal studied was observed to contain a fractional water molecule of crystallization as indicated by the NMR spectrum. The refined occupancy factor for this oxygen atom was 0.38. Refinement converged with R_1 (based on F). =0.0564 for 4202 observed reflections [$I>2\sigma(I)$].

Example Set 2

The reversible formation of secondary complexes of compound 1 was monitored in acetonitrile by UV/Vis spectroscopy employing a range of mono-, di-, and trivalent cations. The monocationic alkali series, Li^+, Na^+ and K^+ (as the triflate salts), exhibit a surprisingly large variation in the binding properties. Thus, Li^+ binding exhibits isosbestic behavior (Figure 3) and a mole ratio plot indicates that 2.5 equivalents of Li^+ are required for complete lithiation. Titrations were carried out in triplicate ([compound 1] = 0.30, 0.27 and 0.14 mmol L^{-1}, $\log K_{25}°=5.02\pm0.06$). In comparison, the mole ratio plot for Na^+ binding (Figure 9) shows that there are two binding processes, as evidenced by a first plateau beginning at 8 equivalents of Na^+ and a second plateau beginning at 47 equivalents. It is believed that the first binding event occurs at the bidentate site and the second binding event occurs at a monodentate amide *O*-atom. The UV/Vis spectrum does not change on addition of K^+ (up to 60 equiv). The UV/Vis changes nonisosbestically on addition of Ba^{2+} (Figure 13) in such a manner as to suggest that more than one compound 1 anion can bind to Ba^{2+}; Ba^{2+} binding is strong with the mole ratio plot indicating that the endpoint is reached at 1.3 equivalents of the Ba^{2+}. Similarly, Sc^{3+} binding exhibits nonisosbestic behavior, but only one equivalent is required to reach the endpoint (Figure 14). Unfortunately, the cyclic voltammetric behavior of the system represented by compound 1 is not electrochemically reversible for any switching ion. However, cyclic voltammetric studies of the planar, four-coordinate Co^{III} analogue of compound 1 show electrochemically reversible electron transfer properties for a variety of secondary ions. For example, under conditions of excess Co^{III} complex,

the dinuclear, trinuclear and tetranuclear species are all observable with Ca^{2+}. From these and electrospray ionization MS studies where the multinuclear ions are also observable, one can conclude that the Co^{III} analogue of compound 1 binds more than once to multiply-charged switching ions. The multiple binding of compound 1 to multiple charged switching ions provides a coherent rationalization for the absence of isosbestic behavior in the UV/Vis binding studies for Ba^{2+}/compound 1 and Sc^{3+}/compound 1. Cumulatively, these results suggest that both the bidentate and amide-*O* binding sites express a significant sensitivity to the charge/size ratio of the secondary ion or ions.

Example Set 3

The susceptibility of the manganyl moiety of the compound 1 system to secondary ion perturbation can be illustrated by the effect of Li^+ binding on the ν(Mn≡O) band in the IR spectrum. To obtain an IR region free of macrocyclic ligand bands, the ^{18}O-labeled manganyl was examined; this was produced by stirring [Et_4N][compound 1] in a mixture of $CH_3CN/H_2{}^{18}O$ (1:1; 98% ^{18}O) for three weeks at room temperature. The $\nu(Mn{\equiv}{}^{18}O)$ band for the Li^+ free and Li^+ bound species are shown in Figure 4; $\nu(Mn{\equiv}{}^{18}O)$ shifts from 939 cm^{-1} in the parent complex to 954 cm^{-1} in the Li^+ complexed species. This blue shift of 15 cm^{-1} implies that Li^+ binding induces a substantial drop in the donor capacity of the macrocyclic tetraamido-*N* ligand, a drop that is compensated for by an increase in donation from the oxo ligand with its associated increase in oxo binding energy. One can infer that the electrophilicity of the oxo ligand should also increase significantly on secondary cation binding.

Example Set 4

The effects of the different switching ions on reactivity were first examined by studying a proof of concept oxidation, namely the oxidation of triphenylphosphine to triphenylphosphine oxide. The reactions with different switching ions were monitored by UV/Vis spectroscopy at 15 °C in acetonitrile under air employing one equivalent of compound 1 and 100 equivalents of triphenylphosphine. Switching ions were added as the triflate salts (5 and 60 equiv);

the reactions were performed at least in triplicate. Formation of the oxidation product, triphenylphosphine oxide, was demonstrated by ^{1}H NMR spectroscopy and by IR spectroscopy in the ν(P=O) region. The results are presented in Figure 5; the relative rates are normalized against the rate of oxidation of triphenylphosphine by the parent compound 1 in the absence of a switching ion. As was found for secondary cation binding to compound 1, the switching effect on the rate of phosphine oxidation is strongly dependent on the nature of added switching ion. Oxidation of triphenylphosphine to triphenylphosphine oxide under the conditions of the UV/Vis experiment by unswitched compound 1 is slow; the reaction takes several thousand seconds to reach completion. The rates relative to the unswitched rate in the presence of five equivalents of various switching ions were found to be the following: Na^+=3, Ba^{2+}=5, Mg^{2+}=7, Li^+=13, Zn^{2+}=24, Sc^{3+}=1244. As noted above it was found that the Na^+ ion is unique among the switching ions studied in possessing an appreciable second binding to compound 1. The relative rates of triphenylphosphine oxidation by compound 1 with different switches reflect this finding. Thus, no increase in the rate of triphenylphosphine oxidation was found upon an increase in the switching ion: compound 1 ratio from 5:1 to 60:1 for Mg^{2+} or Zn^{2+}. Small increases are found when this ratio increase is enacted for Ba^{2+} (1.2 fold), Li^+ (2 fold) and Sc^{3+} (1.3 fold). In contrast, an increase in the Na^+: compound 1 ratio from 5:1 to 60:1 produces a 169-fold increase in the rate of phosphine oxidation. Moreover, addition of K^+ (up to 60 equiv) does not perturb the oxidation rate of the parent unswitched compound 1 reinforcing what was noted above that K^+ does not appear to bind to the switching site in a concentration regime that can be readily studied.

The oxo-transfer rate increases presented above for a trivial oxidation signal genuinely useful properties. We have also investigated the reactivity of compound 1 as an O-atom transfer agent for the electron-rich olefin, tetramethylethylene.

Example 5

A mixture of [Ph_4P]compound 1 (1 equiv), $ZnTf_2$ (4.5 equiv), 2,3-dimethyl-2-butene (tetramethylethylene, 132 equiv), and TBHP (90%, 266 equiv) in

acetronitrile-d_3 was monitored at 50°C via ^{13}C spectroscopy until all of the olefin had been consumed (48 hr). The only observable product was 2,3-dimethylbut-3-en-2-ol (>98%); the reaction was performed in triplicate. ^{13}C NMR (acetonitrile-d_3): (See Figure 15) 2,3-dimethylbut-3-en-2-ol; δ 19.5, 29.3, 73.3, 108.7, 153.3. *See*, R. W. Murray, W. Kong, S. N. Rajadhyaksha, *J. Org. Chem.* 58, 315-321 (1993). *See* Fig. 15.

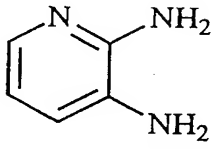
The product solution was also analyzed by GC/MS which confirmed the presence of 2,3-dimethylbut-3-en-2-ol as the only olefin-derived product. The product, the generated *tert*-butanol, and the remaining TBHP had the same relative abundance indicating a very clean stoichiometric and selective reaction. Significantly, except for minor amounts of decomposition, the unemployed TBHP remained unconsumed and addition of further olefin resulted in the recommencement of the catalytic oxidation process. UV/Vis analysis of the catalysis solution indicated the quantitative presence of compound 1 throughout and after the catalytic oxidation. While trace amounts of other products, apparently derived from the TBHP, were detectable in the ^{13}C NMR spectra, a spent reaction solution in acetone-d_6 remained essentially unchanged upon standing in an NMR tube on the bench top for nine months; after this time, it was found to contain 2,3-dimethylbut-3-en-2-ol, *tert*-butanol, TBHP and its acetone adduct in the same relative ratios that were established at the end of the reaction and nothing else. A control system without compound 1 consisting of $ZnTf_2$ (1 equiv), 2,3-dimethyl-2-butene (30 equiv), and TBHP (90%, 64 equiv) in acetonitrile-d_3 was also monitored at 50°C for five days by ^{13}C NMR spectroscopy; no change was observed. When the reaction conditions were changed by raising the temperature to 70° C and using deuterated acetonitrile as the solvent, the same five characteristic peaks shown in Fig. 15 for 2,3-dimethylbut-3-en-2-ol were present. Thus, compound 1 presents a mild, exceptionally selective and extraordinarily stable catalytic O-atom transfer system.

As part of Nature's design, enzymes often arrange multiple reactions precisely in both time and space to achieve a targeted selectivity. While modern

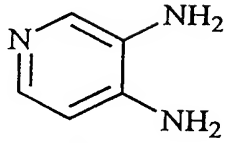
chemistry includes rich insight into how to arrange reactions in space to achieve selectivity, the mastering of selectivity by the deliberate arrangement of multiple reactions in time is novel territory. Using the variations in reactivity, spatial orientation and size afforded by the oxidation catalysts described herein, a ligand system can be designed for organizing in sequence and reaction site more than one oxidation reaction to achieve a targeted reactivity and selectivity. The ligand systems of the present invention are significantly resistant to oxidative decomposition such that they provide very long-lived and reusable catalysts. The synthetic procedures to produce numerous variations of compound 1 have been refined such that the ligand can be produced in a two-step procedure from the series of diamines shown in Table 1 according to the procedures set forth in Gordon-Wylie et al., incorporated herein by reference, as modified by the substitution of the diamines of Table I for the diamines described in the Gordon-Wylie syntheses. It is important to realize that the approach presented clearly expands the range of reactivity achievable for the environmentally desirable transition metals, such as manganese, by allowing one to deliberately increase the reactivity of an otherwise slow O-atom transfer agent or, more generally, reagents such as compound 1 and its variants which are designed to assemble more than one reaction to oxidation catalyst achieve a reactivity objective may become essential in the greening of chemistry. They make possible the novel methods of the present invention for making environmentally desirable catalytic elements perform all the tasks necessary to replace the environmentally undesirable elements currently in use. The approach of arranging multiple reactions in time holds enormous promise for dealing with difficult reactivity problems such as for obtaining otherwise inaccessible green reagents, especially oxidants, and for achieving enantioselectivity and chemoselectivity in oxidations that have proven to be resistant to less ambitious development approaches.

TABLE I

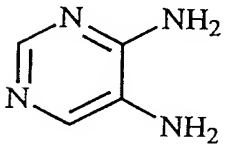
Aza Aryl Substitutions



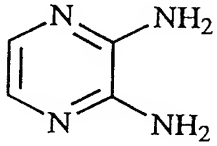
The parent complex (pyridine-)



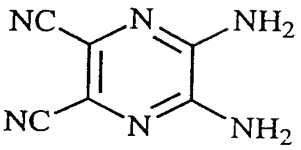
pyridine-



pyrimidine-

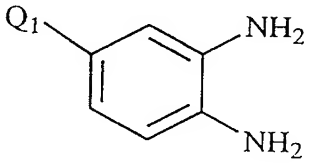


pyrazine-

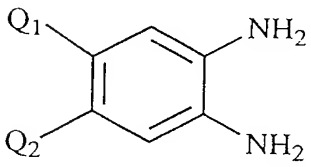


dicyano-pyrazine-

Simple Aromatic Substitutions

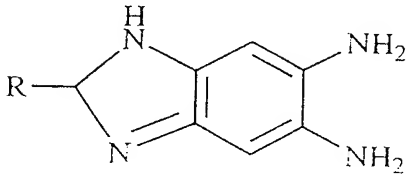


$Q_1 = NH_2$, RNH, R_2N, CO_2H, SO_3H, OH, SH

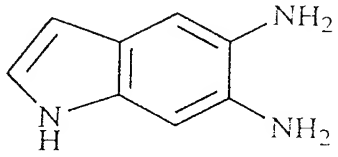


$Q_1 = NH_2$, RNH, R_2N, CO_2H, SO_3H, OH, SH
$Q_2 = NH_2$, RNH, R_2N, CO_2H, SO_3H, OH, SH

Other Switching Substituents



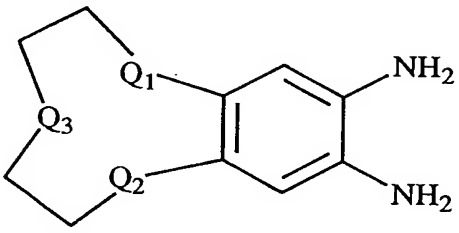
Benzimidazole-



Indole-

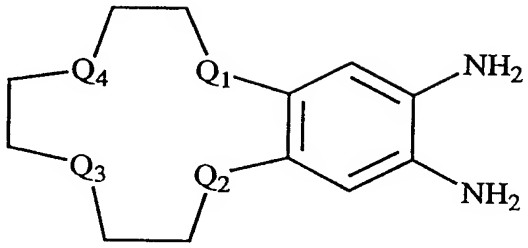
TABLE I Continued

Substituted Crown Derivatives



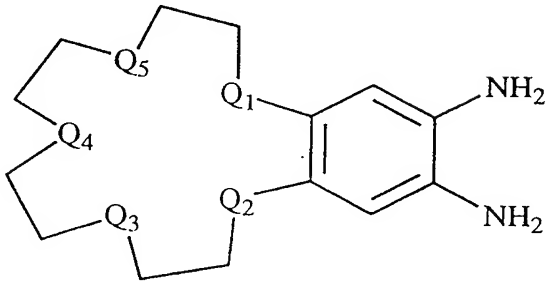
Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S

substituted -benzo-9-crown-3-



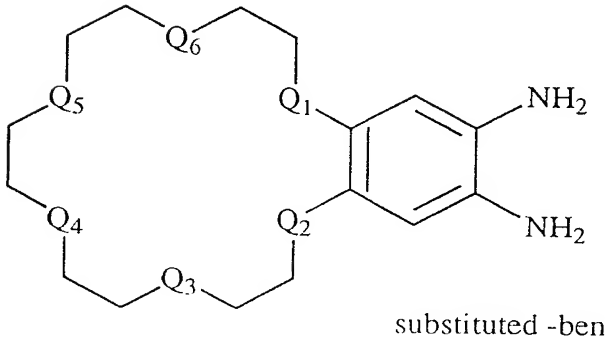
Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S

substituted -benzo-12-crown-4-



Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S
Q_5 = NH, NR, O, or S

substituted -benzo-15-crown-5-



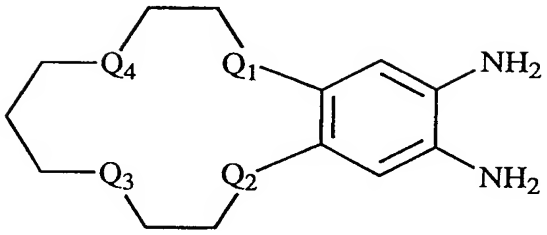
Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S
Q_5 = NH, NR, O, or S
Q_6 = NH, NR, O, or S

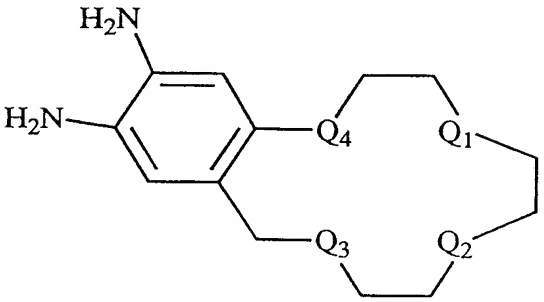
substituted -benzo-18-crown-6-

TABLE I Continued

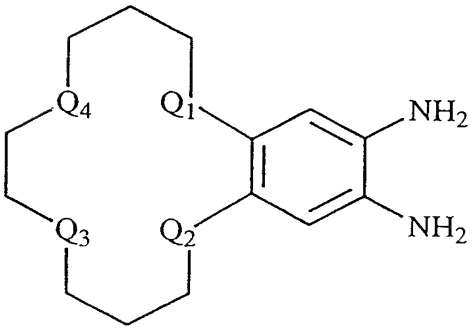
Other Cryptand Ligands

Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S

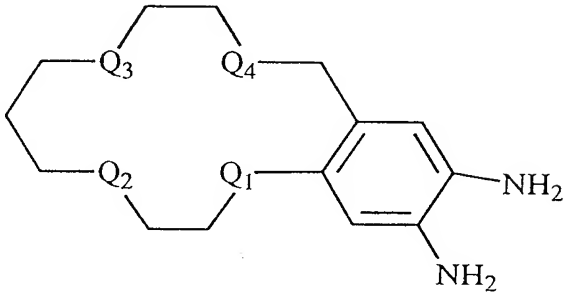




Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S



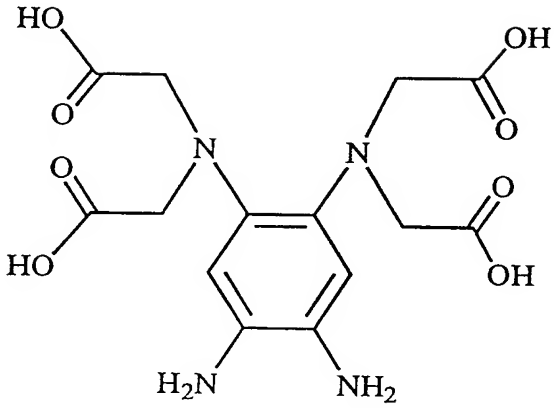
Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S



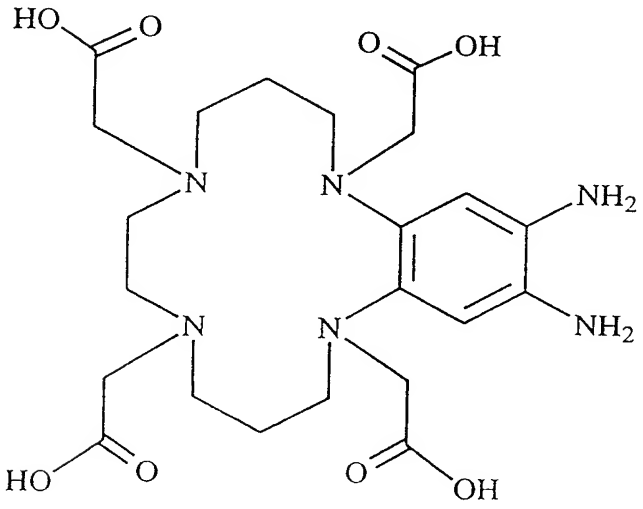
Q_1 = NH, NR, O, or S
Q_2 = NH, NR, O, or S
Q_3 = NH, NR, O, or S
Q_4 = NH, NR, O, or S

TABLE I Continued

Derivatives of EDTA



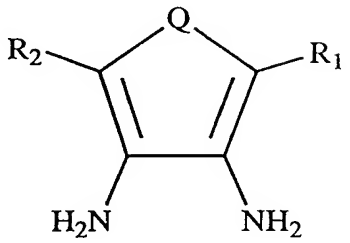
Ethylene Diamine Tetra Acetic Acid-

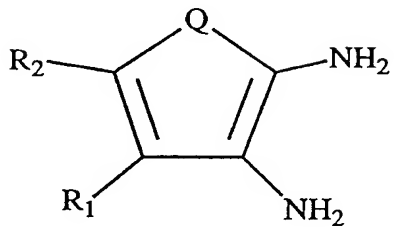


Tetra Aza Cyclo Tetra Decane Tetra Acetic Acid-

TABLE I Continued

Five Membered Rings

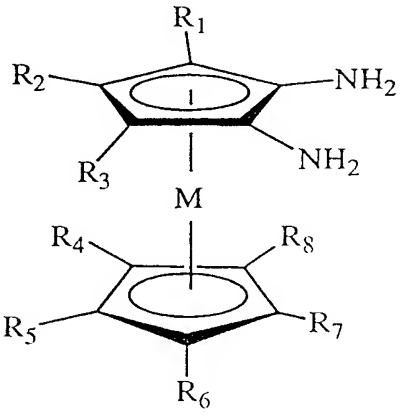


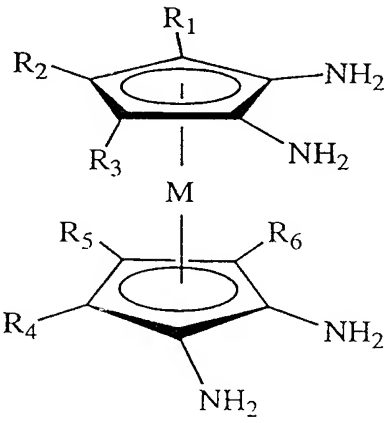


Q = NH (pyrrole-), S (thiophene-), O (furan-), CH_2 (cyclopentadiene-), RCH (substituted cyclopentadienyl with R= alkyl, aryl)

R_1 = H, Alkyl, Aryl, Alkenyl, Halo
R_2 = H, Alkyl, Aryl, Alkenyl, Halo

Five membered ring derivatives





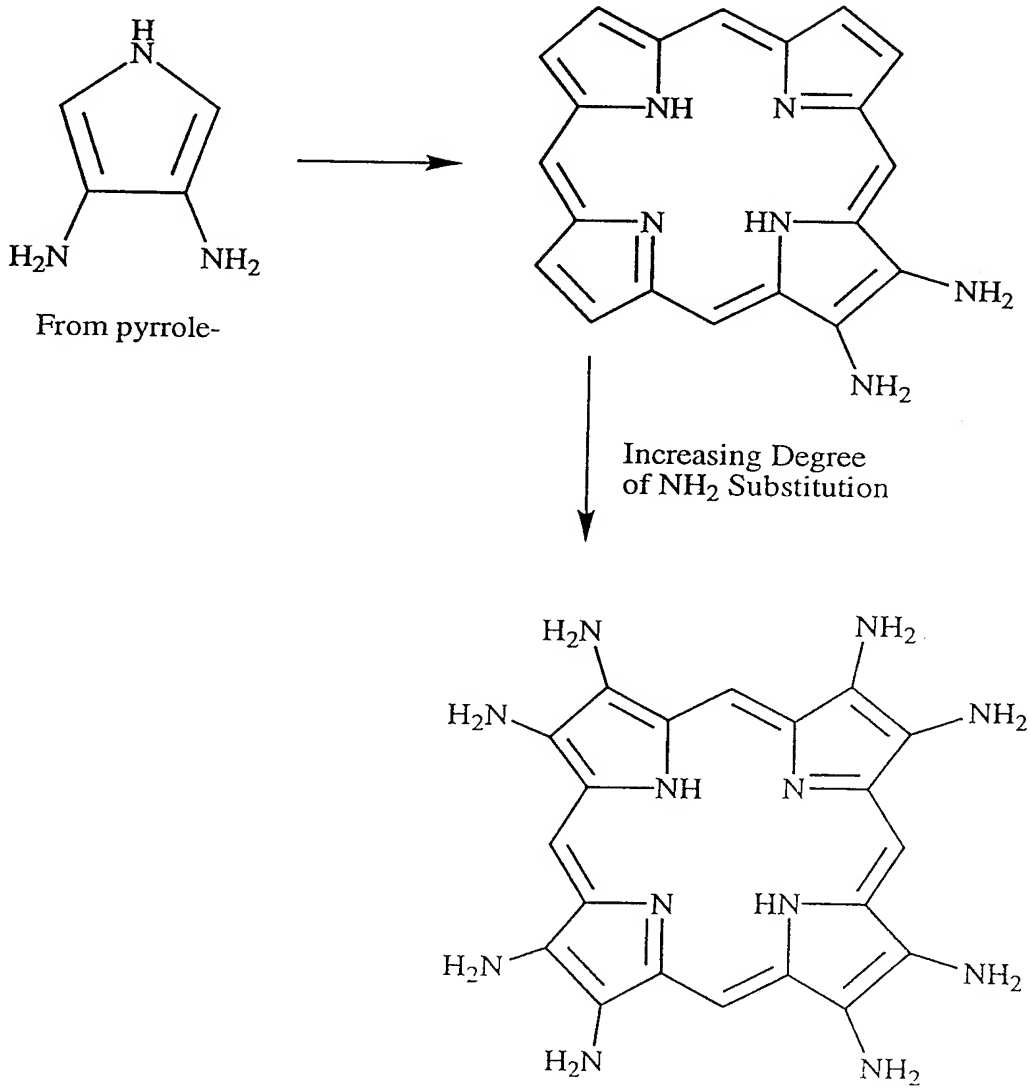
M = V, Cr, Mn, Fe, Co, Ni, Ru, Os, Rh
e.g. for M= Fe one obtains Ferrocene/Ferrocenium switched derivatives

R_1 = H, Alkyl, Aryl, Alkenyl, Halo
R_2 = H, Alkyl, Aryl, Alkenyl, Halo
R_3 = H, Alkyl, Aryl, Alkenyl, Halo
R_4 = H, Alkyl, Aryl, Alkenyl, Halo

R_5 = H, Alkyl, Aryl, Alkenyl, Halo
R_6 = H, Alkyl, Aryl, Alkenyl, Halo
R_7 = H, Alkyl, Aryl, Alkenyl, Halo
R_8 = H, Alkyl, Aryl, Alkenyl, Halo

TABLE I Continued

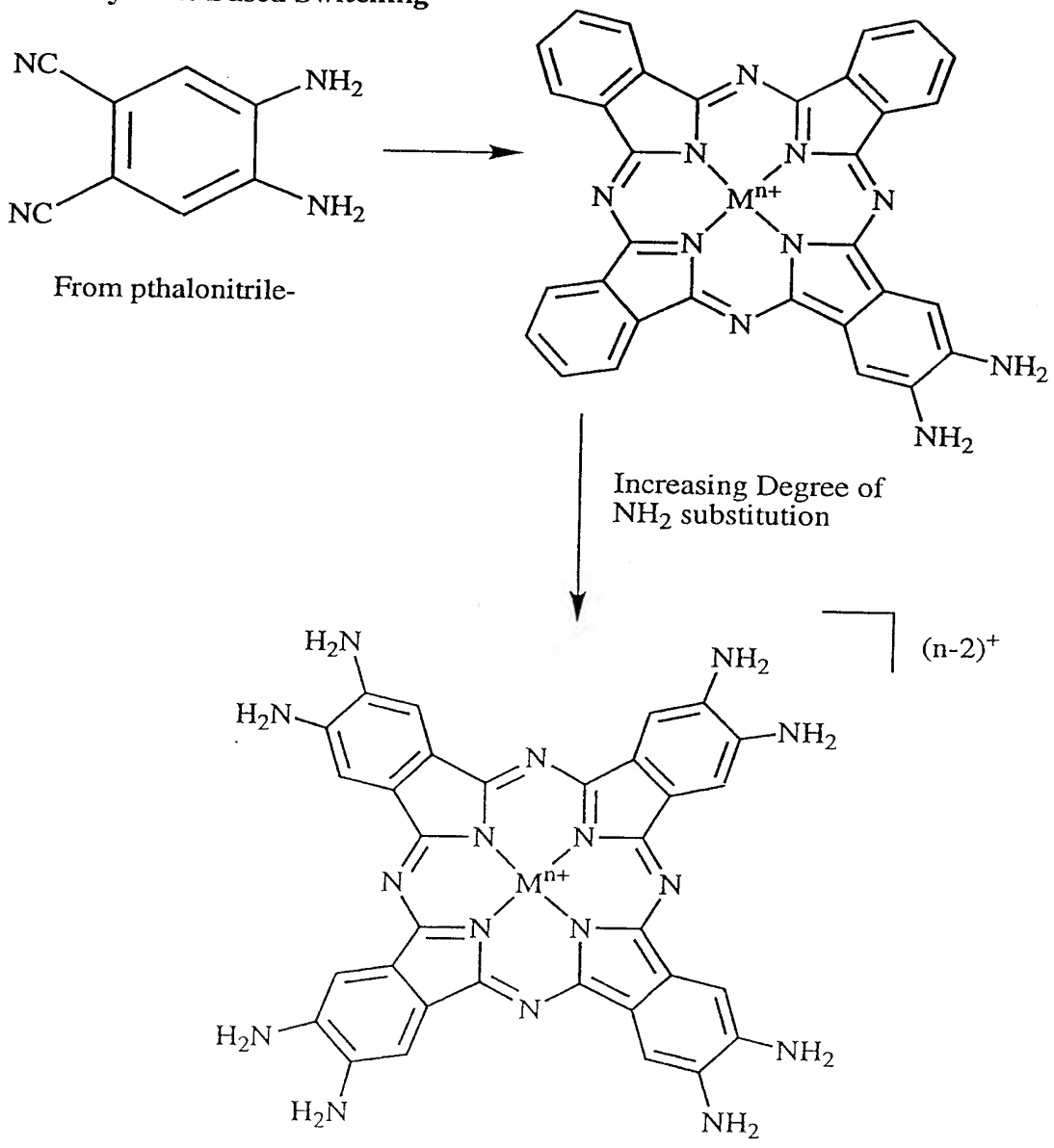
Porphyrin Based Switching



Switching can be accomplished via metallation of the porphyrin, via oxidation state change of the free base porphyrin or the metallated porphyrin, via change in the axial ligation of the metal porphyrin, optically etc.

TABLE I Continued

Pthalocyanine Based Switching



Switching can be accomplished via metallation of the free base pthalocyanine, oxidation state change of the metallated pthalocyanine, axial ligation of the metal pthalocyanine complex, optically etc.

TABLE I Continued

Bi-Pyridyl Based Systems

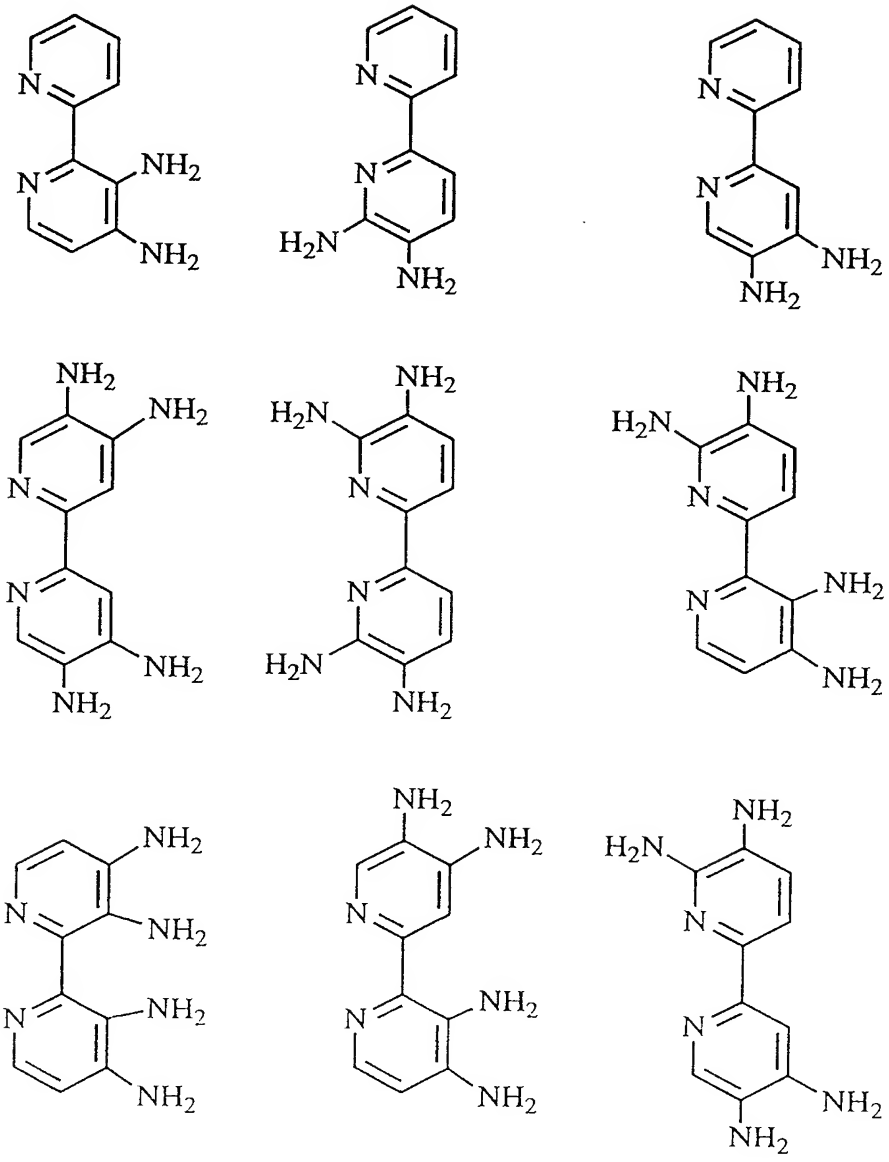


TABLE I Continued

Phenanthroline Based Systems

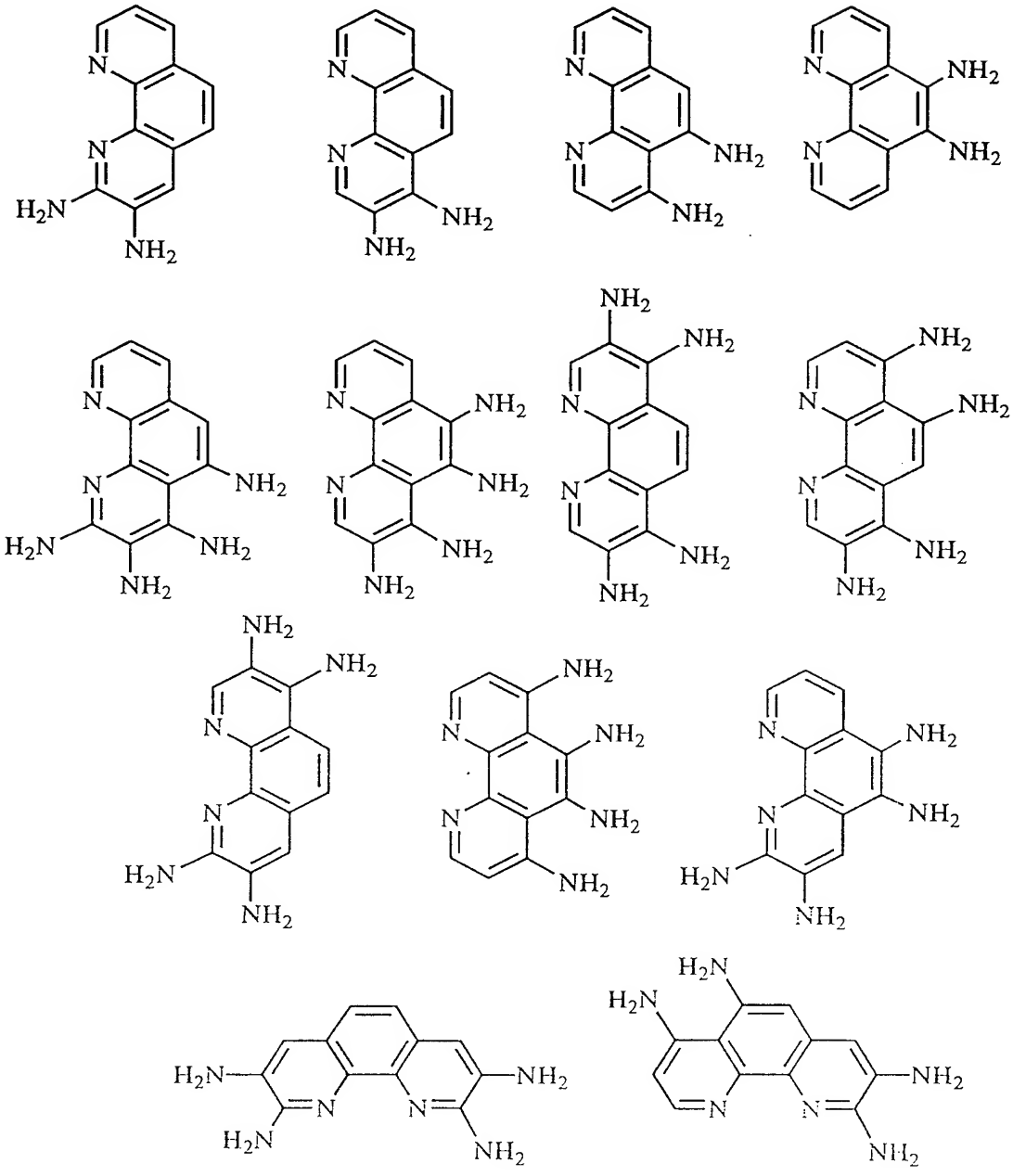
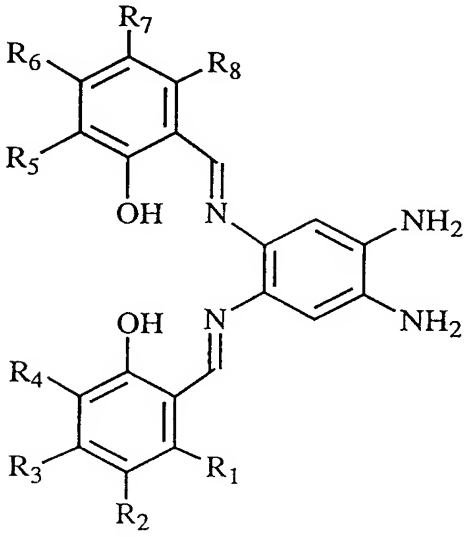
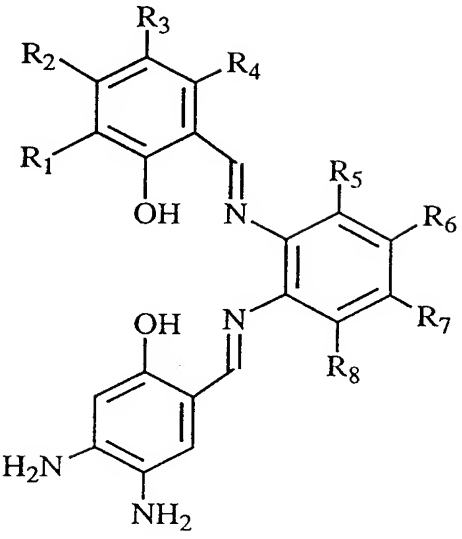
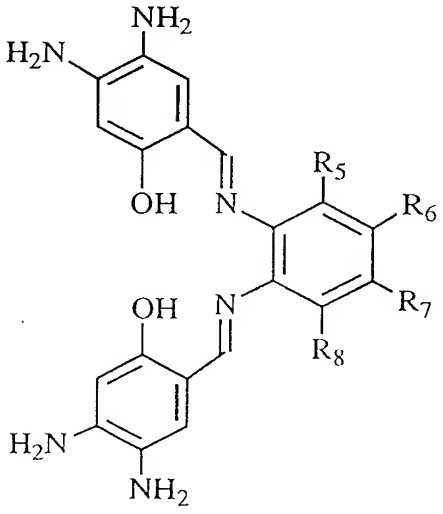


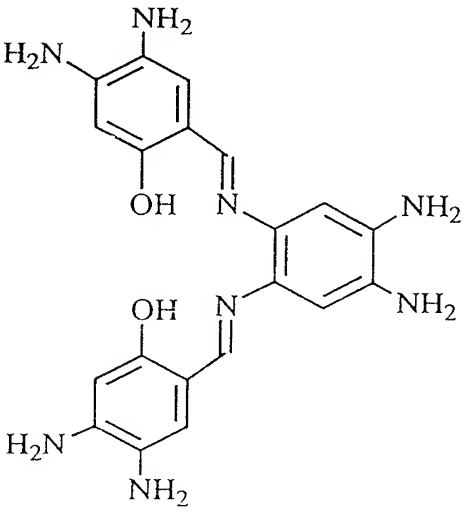
TABLE I Continued

Salen Based Switching Systems









What we claim is:

1. A method of transferring oxygen to at least one oxidizable site on a target compound having a plurality of oxidizable sites, the method comprising:

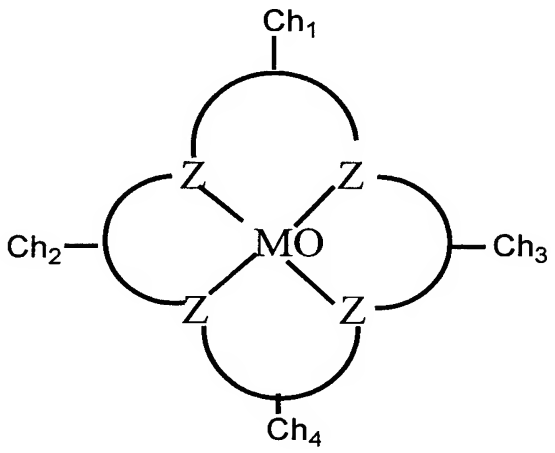
selectively oxidizing an oxidizable site on a target compound having a plurality of oxidizable sites therein by reacting in solution:

the target compound;

a source of oxygen atoms;

a source of a Lewis acid; and,

a catalyst having the structure



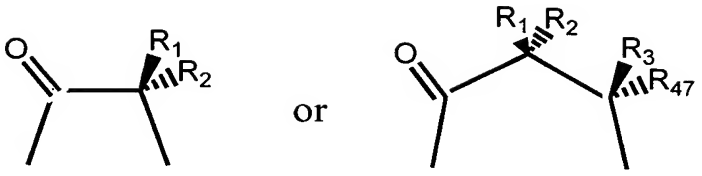
wherein:

Z is N or O and at least one Z is N;

MO is a transition metal-oxo species;

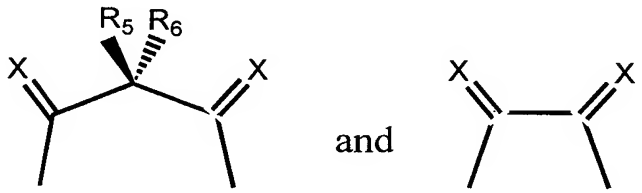
Ch_1 is selected from the group consisting of pyridine, pyrimidine, pyrazine, dicyano-pyrazine, mono-, di-, tri- or tetra- substituted benzene, benzimidazole, benzoquinone, mono- or di- iminobenzene, indole, substituted crown derivatives, cryptand ligands, EDTA derivatives, five-membered rings and five-membered ring derivatives, porphyrin derivatives, metallated-pthalocyanine based systems, bi-pyridyl-based systems, phenanthroline-based systems and salen-based systems

Ch_2 and Ch_3 each represent a unit joining the adjacent Z atoms comprised of



wherein R_1, R_2, R_3, and R_4 pairwise and cumulatively are the same or different and each is selected from the group consisting of alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halogen,haloalkyl, perhaloalkyl, CH_2CF_3 and CF_3 or R_1, R_2, R_3 and R_4 together form a substituted or an unsubstituted benzene ring, or the paired R substituents of the R_1, R_2 or the R_3, R_4 pairs together form a cycloalkyl or a cycloalkenyl ring; and,

Ch_4 is a unit joining the adjacent Z atoms selected from the group consisting of



wherein R_5 and R_6 are the same or different, linked or nonlinked, and each is comprised of hydrogen, ketones, aldehydes, carboxylic acids, esters, ethers, amines, imines, amides, nitro, sulphonyls, sulfates, phosphoryls, phosphates, silyl, siloxanes, alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halo, CH_2CF_3 or CF_3 , or the paired R substituents of the R_5, R_6 pair together form a cycloalkyl or a cycloalkenyl ring; with substituents chosen as for unlinked R_5, R_6 and,

allowing the reaction to proceed for a period of time sufficient to oxidize at least one oxidizable site of the target compound.

2. The method recited in the claim 1 wherein the Lewis acid is selected from the group consisting of proton, alkali, alkaline earth, rare earth or transition metal or main group metal ions.
3. The method of claim 1 wherein the plurality of oxidizable sites in the target compound differ from each other in relative reactivity and the Lewis acid (is

selected to selectively) activates the catalyst by forming a cation-catalyst complex for oxidizing one oxidizable site on the target compound.

4. The method of claim 3 further including the steps of:

identifying a series of oxidizable sites on the target compound, having reactivities ranging sequentially from generally the highest relative reactivity for a beginning set of oxidizable sites of the series of oxidizable sites to the lowest relative reactivity for an ending set of oxidizable site of the oxidizable sites in the series of sites; and,

(a) adding to the solution a first cation for activating the catalyst to form a first cation-catalyst complex having a first reactivity, the first reactivity of the first cation-catalyst complex sufficient to selectively oxidize the first set of oxdizable sites in preference to oxidizing other oxidizable sites in the target compound;

(b) allowing the oxidation reaction to proceed for a period of time sufficient to oxidize each beginning oxidizable site on the target compound such that the second set of oxidizable sites in the series has the highest relative reactivity of the oxidizable sites remaining in the series of sites;

(c) optionally removing the first cation from the solution;

(d) adding a second cation to the solution, the resulting cation-catalyst complex having a second reactivity sufficient to selectively oxidize the second set of oxidizable sites;

(e) allowing the oxidation reaction to proceed for a period of time sufficient to permit the oxidation of the second set of oxidizable sites on the target compound such that any next oxidizable sites in the series of oxidizable sites on the target compound has the highest relative reactivity of the oxidizable sites remaining in the series of sites;

(f) optionally removing the second cation from the solution;

(g) repeating steps (d) to (f) for each successive oxizable site in the series of oxidizable sites on the target compound by sequentially adding selected cations to the solution, allowing the oxidation to proceed and removing

the selected cation from the solution before the next selected cation is added, each successive cation added to the solution having progressively higher reactivities to effect the sequential oxidation of the oxidizable sites in the series of oxidizable sites until the ending oxidizable site is oxidized.

5. The method recited in claim 4 wherein the set of oxidizable sites includes one oxidizable site.

6. The method recited in claim 4 wherein the set of oxidizable sites includes more than one oxidizable site.

7. The method recited in claim 1 wherein the target compound has at least one prochiral oxidizable site and the Lewis acid catalyst complex has chirality such that it catalyzes the enantioselective oxidation of said at least one oxidizable site.

8. The method recited in claim 7 wherein the oxidizable site is a prochiral phosphorous containing compound.

9. The method recited in claim 1 wherein the oxidizable sites are olefins

10. The method recited in claim 7 wherein the oxidizable sites are alkynes.

11. The method recited in claim 7 wherein the transition metal of the catalyst is manganese.

12. The method of claim 7 wherein the transition metal of the catalyst is iron.

13. The method of claim 7 wherein the transition metal is selected from the group consisting of Groups 6, 7, 8, 9, 10, and 11 of the periodic table of the elements or those having an oxidation state of I, II, III, IV, V, VI, VII or VIII.

14. The method recited in claim 1 wherein the oxidizable sites are alkynes.

15. The method recited in claim 1 wherein the oxidizable sites are olefins.

16. The method recited in claim 1 wherein the transition metal of the catalyst is manganese.

17. The method of claim 1 wherein the transition metal of the catalyst is iron.

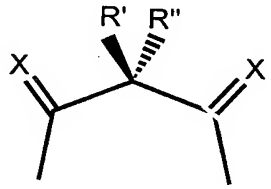
18. The method of claim 1 wherein the transition metal is selected from the group consisting of Groups 6, 7, 8, 9, 10, and 11 of the periodic table of the elements or those having an oxidation state of I, II, III, IV, V, VI, VII or VIII.

19. The method recited in claim 1 wherein the Lewis acid is selected from the group of atoms of the lanthanide series.

20. The method recited in claim 1 wherein the Lewis acid is selected from the group of atoms of the actinide series.

21. The method of claim 1 wherein the cation is selected from the group consisting of Li^+, Na^+, Zn^{2+}, Mg^{2+}, Ca^{2+}, Ba^{2+}, Sc^{3+}, Rh^{3+} and Ru^{2+}.

22. The method recited claim 1 wherein the metal of the metal-oxo species is an iron and Ch_4 is



wherein:

Z is the metal complexing atom, preferably N; X is a functionality resistant to oxidation when the metal complex is in the presence of an oxidizing medium; and

R' and R" are the same or different and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly within R' and R" and with the cyclic carbon to which they are bound, are sterically hindered and are conformationally hindered such that oxidative degradation of the metal complex is restricted in the presence of an oxidizing medium.

23. The method recited in claim 22 wherein R_5 and R_6 are each selected from the group consisting of hydrogen, halogen, methyl, CF_3, and if linked, cyclobutyl, cyclopentyl, cyclopropyl, or cyclohexyl.

24. A method of transferring oxygen to an oxidizable site on a target compound comprising:

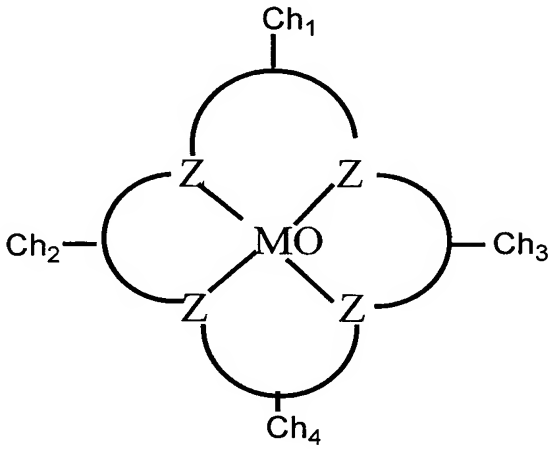
selectively oxidizing an oxidizable site on a target compound having one prochiral oxidizable site by reacting in solution:

the target compound;

a source of oxygen atoms;

a source of a Lewis acid; and,

a catalyst for forming a complex with the Lewis acid, said complex having chirality and said catalyst having the structure



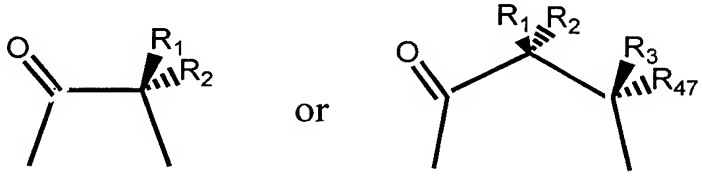
wherein:

Z is N or O and at least one Z is N;

MO is a transition metal-oxo species;

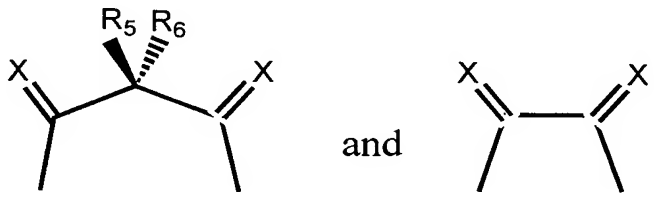
Ch_1 is selected from the group consisting of pyridine, pyrimidine, pyrazine, dicyano-pyrazine, mono-, di-, tri- or tetra- substituted benzene, benzimidazole, benzoquinone, di- iminobenzene, indole, substituted crown derivatives, cryptand ligands, EDTA derivatives, five-membered rings and five-membered ring derivatives, porphyrin derivatives, metallated pthalocyanine-based systems, bi-pyridyl-based systems, phenanthroline-based systems and salen-based systems;

Ch_2 and Ch_3 each represent a unit joining the adjacent Z atoms comprised of



wherein R_1, R_2, R_3, and R_4 pairwise and cumulatively are the same or different and each is selected from the group consisting of alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halogen, haloalkyl, perhaloalkyl, CH_2CF_3 and CF_3 or R_1, R_2, R_3 and R_4 together form a substituted or an unsubstituted benzene ring, or the paired R substituents of the R_1, R_2 or the R_3, R_4 pairs together form a cycloalkyl or a cycloalkenyl ring; and,

Ch_4 is a unit joining the adjacent Z atoms selected from the group consisting of



wherein R_5 and R_6 are the same or different, linked or nonlinked, and each is comprised of hydrogen, ketones, aldehydes, carboxylic acids, esters, ethers, amines, imines, amides, nitro, sulphonyls, sulfates, phosphoryls, phosphates, silyl, siloxanes, alkyl, aryl, alkenyl, alkynyl, alkylaryl, cycloalkyl, cycloalkenyl, alkoxy, phenoxy, halo, haloalkyl, perhaloalkyl, CH_2CF_3 or CF_3 , or the paired R substituents of the R_5, R_6 pair together form a cycloalkyl or a cycloalkenyl ring; and,

wherein the Lewis acid-catalyst complex catalyzes the enantioselective oxidation of said oxidizable site of the target compound.

25. The method recited in claim 24 wherein the Lewis acid is selected from the group consisting of proton, alkali, alkaline earth, rare earth or transition metal ions.

26. The method recited in claim 24 wherein the oxidizable site is an olefin.

27. The method recited in claim 24 wherein the oxidizable site an alkyne.

28. The method recited in claim 24 wherein the oxidizable site is a phosphorous containing compound.

29. The method recited in claim 24 wherein the transition metal of the catalyst is manganese.

30. The method recited in claim 24 wherein the transition metal of the catalyst is iron.

31. The method of claim 24 wherein the transition metal of the metal-oxo species is selected from the group consisting of Groups 6, 7, 8, 9, 10, and 11 of the periodic table of the elements or those having an oxidation state of I, II, III, IV, V , VI, VII or VIII.

32. The method recited in claim 24 wherein the Lewis acid is selected from the group of atoms of the lanthanide series.

33. The method recited in claim 24 wherein the Lewis acid is selected from the group of atoms of the actinide series.

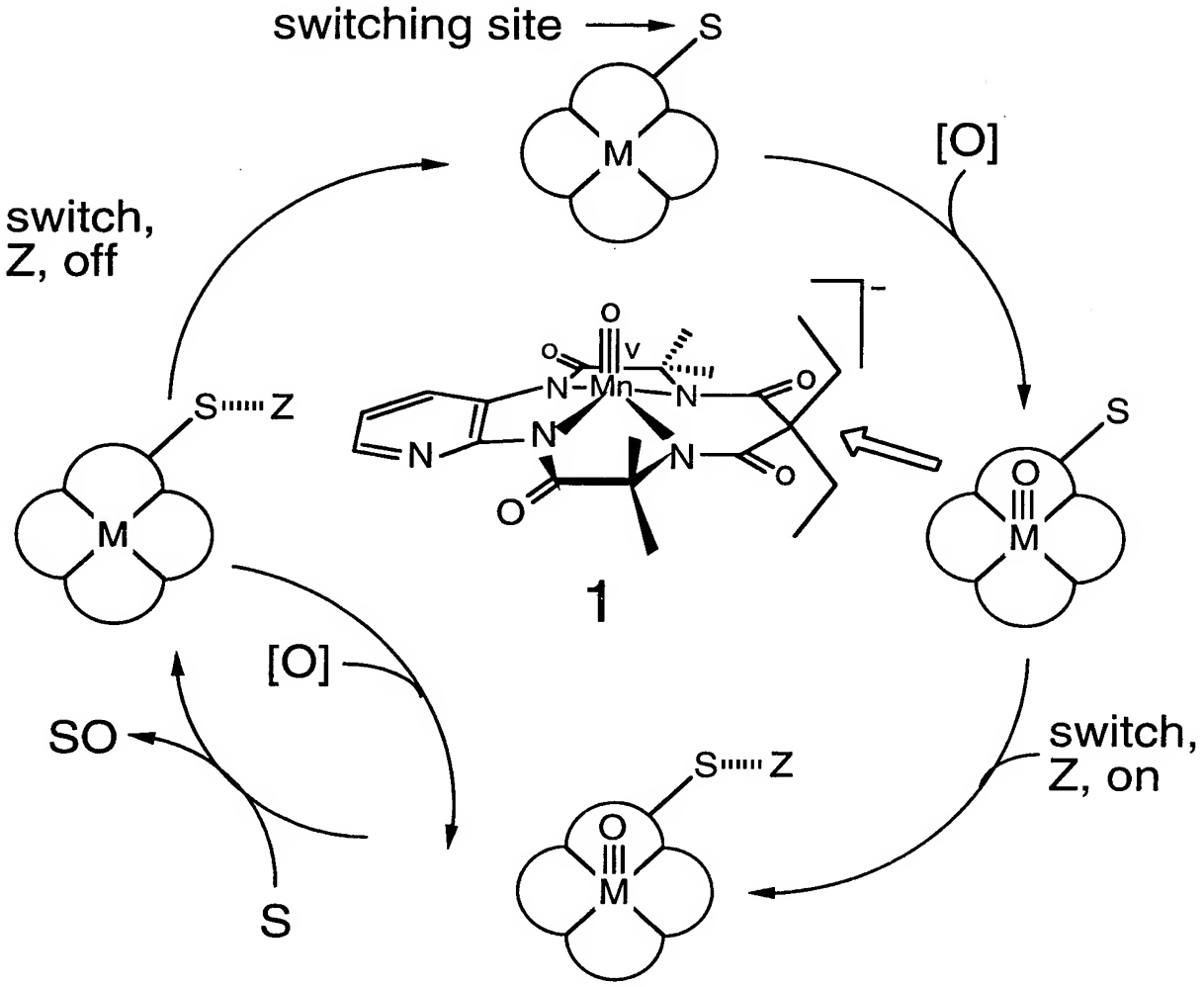

switching site
S
M
[O]
switch,
Z, off
S
Z
M
O
v
N
Mn
N
N
N
N
O
O
O
O
1
S
O
M
[O]
SO
S
S
Z
O
M
switch,
Z, on

FIG. 1

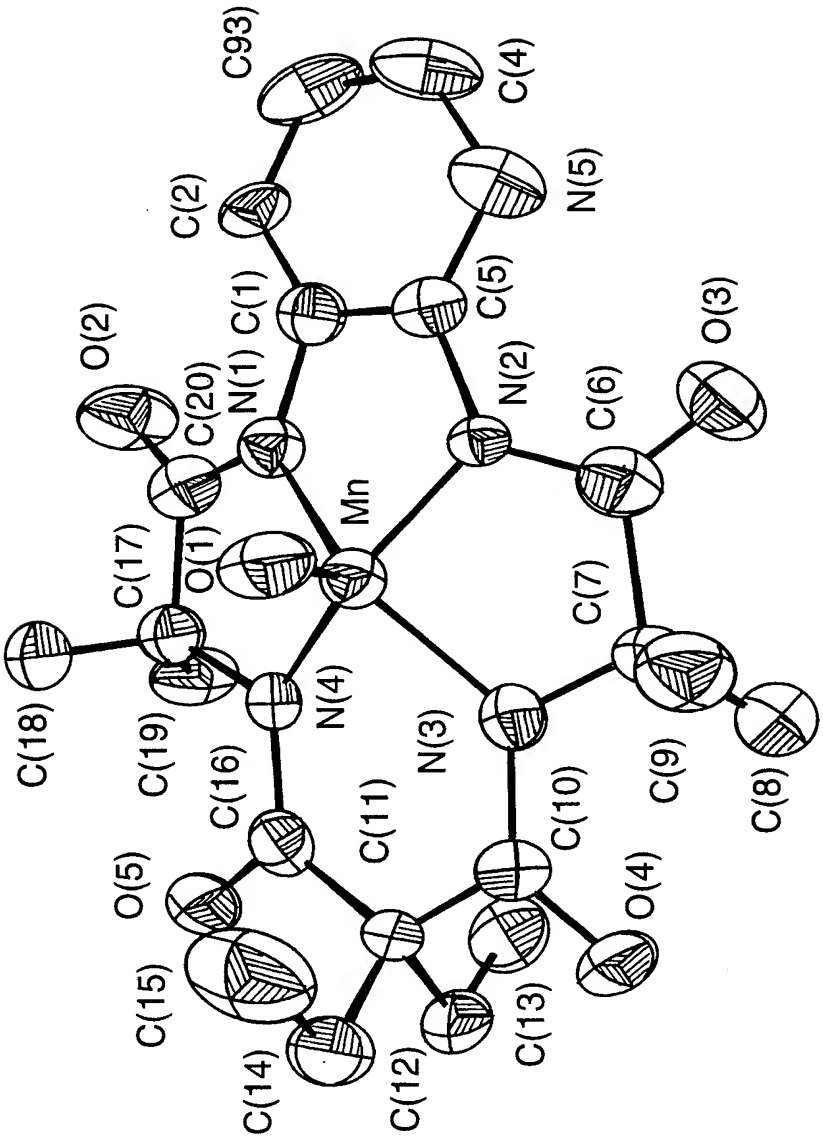

C93
C(4)
C(2)
N(5)
C(1)
C(5)
O(2)
O(3)
N(1)
N(2)
C(20)
C(6)
Mn
O(1)
C(17)
C(7)
C(18)
C(19)
N(4)
N(3)
C(16)
C(11)
C(10)
C(9)
C(8)
O(5)
O(4)
C(15)
C(13)
C(14)
C(12)

FIG. 2

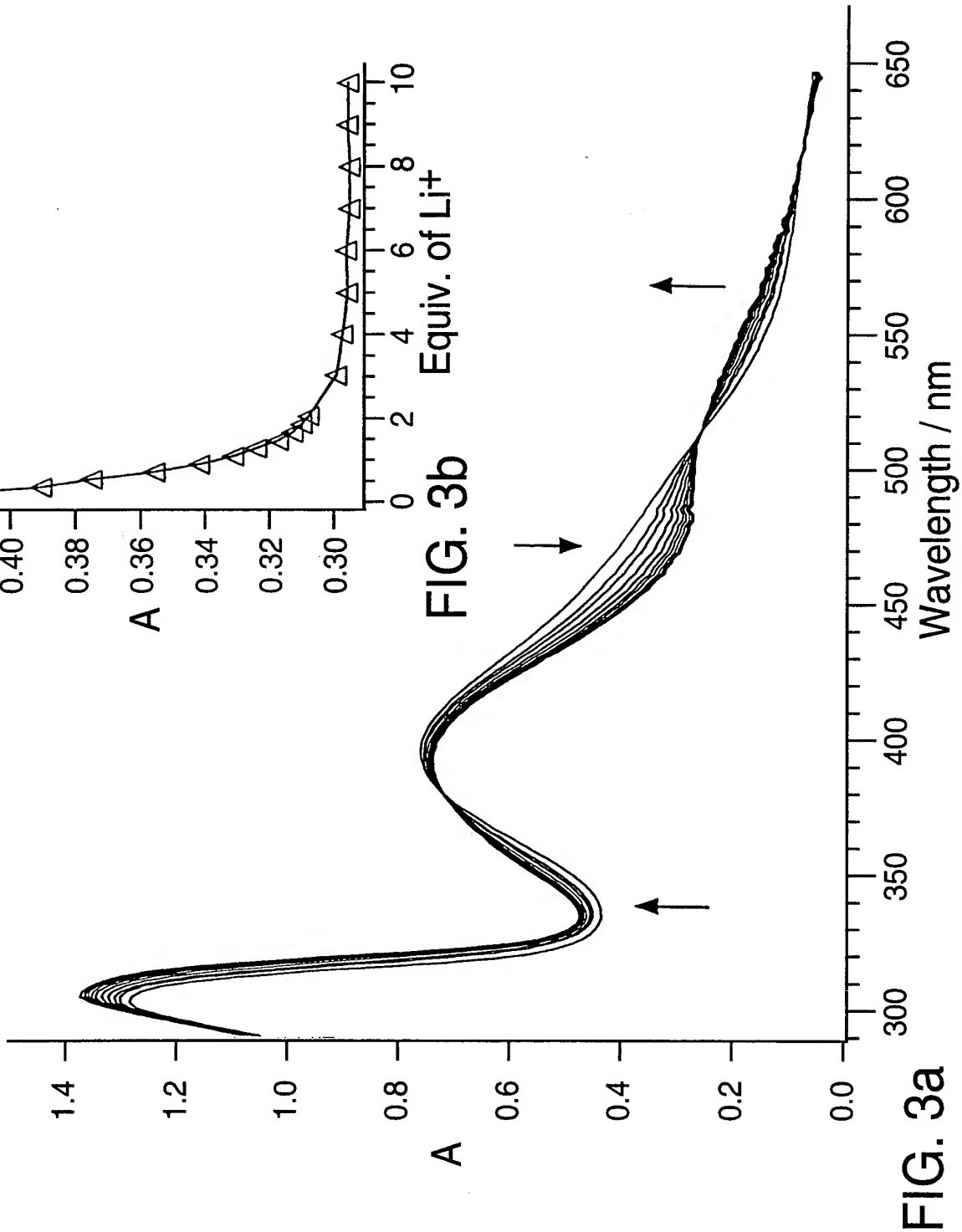

A
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
300
350
400
450
500
550
600
650
Wavelength / nm
A
0.42
0.40
0.38
0.36
0.34
0.32
0.30
0
2
4
6
8
10
Equiv. of Li+

FIG. 3a

FIG. 3b

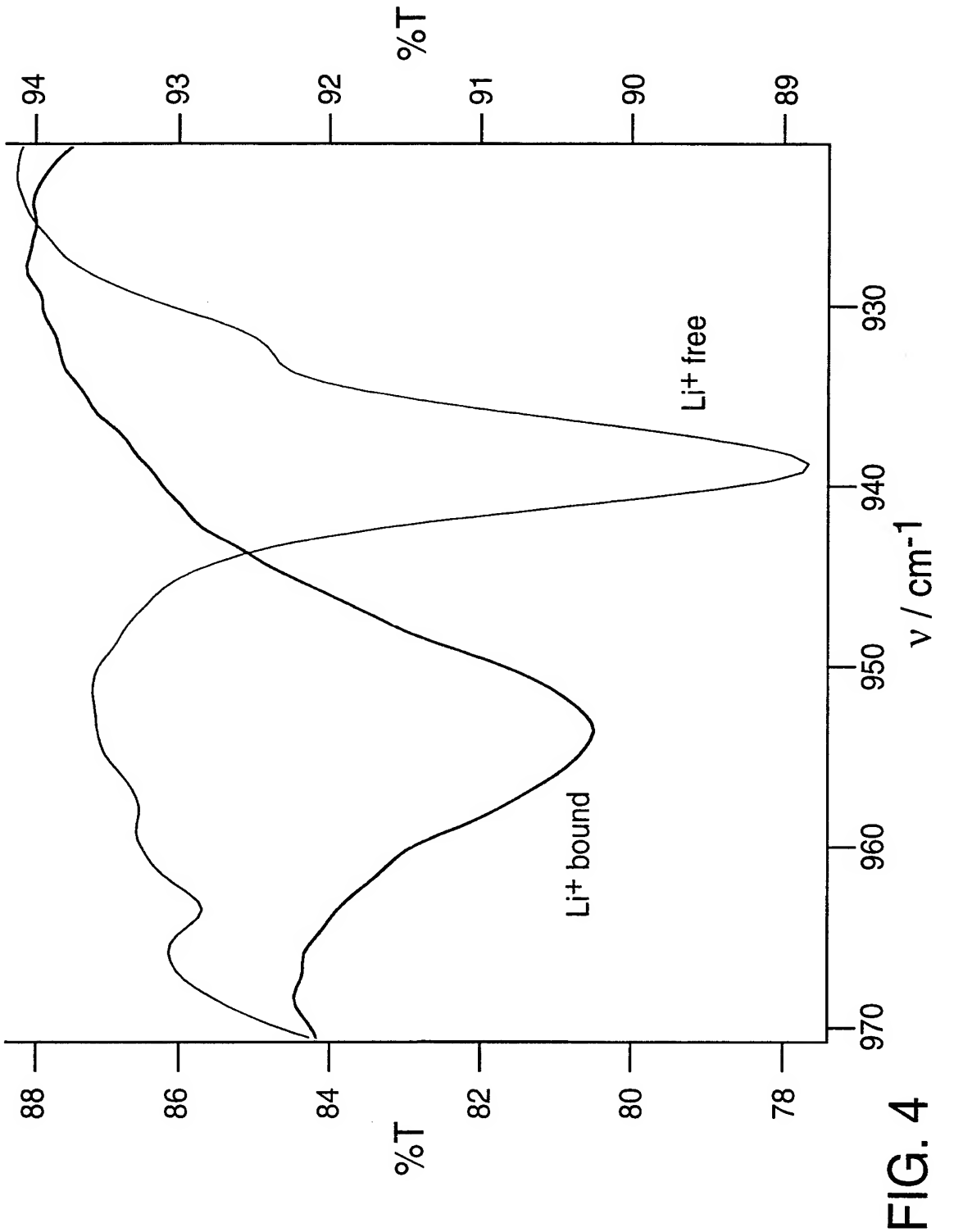

%T
94
93
92
91
90
89
Li+ free
930
940
950
960
970
ν / cm-1
Li+ bound
88
86
84
82
80
78
%T

FIG. 4

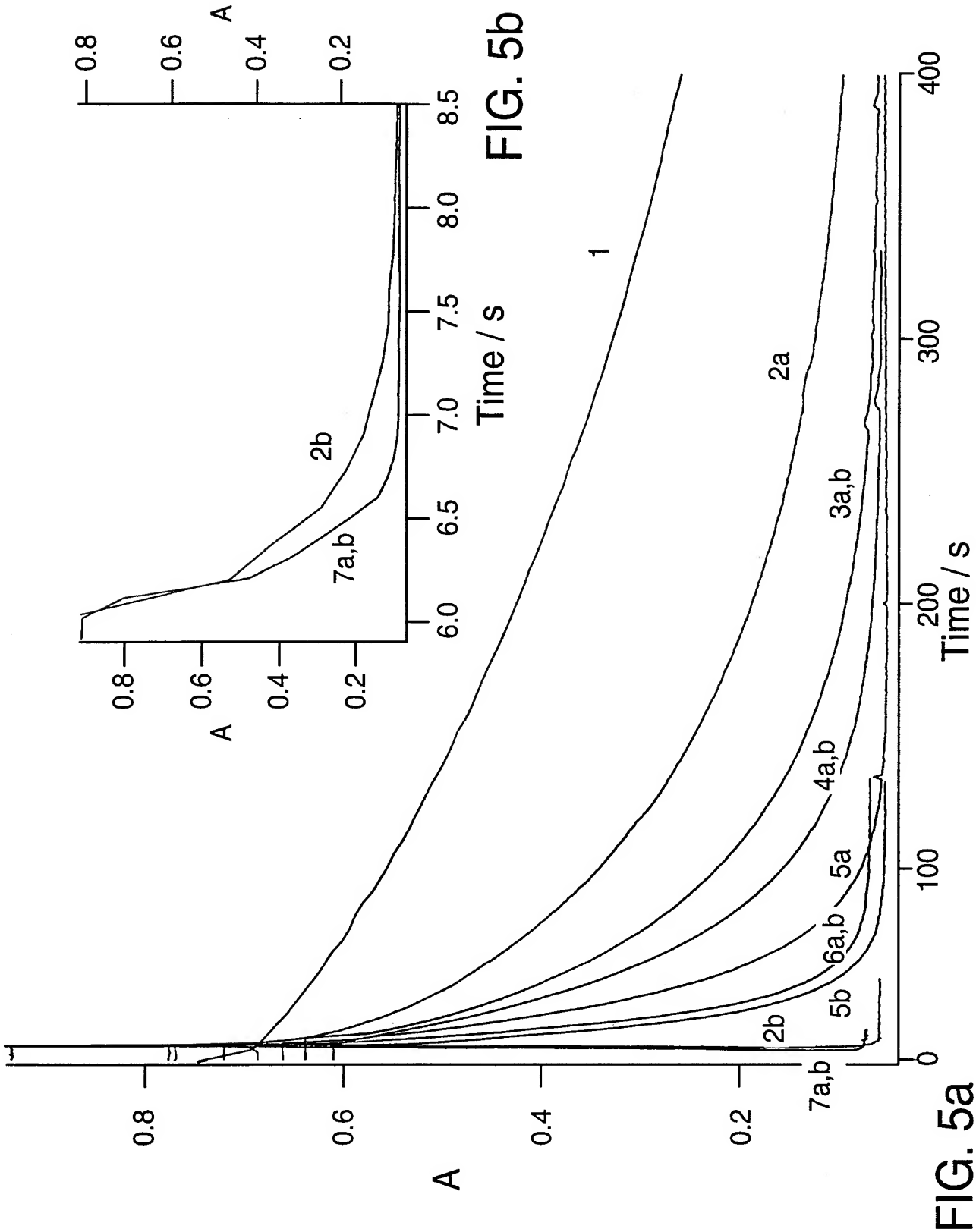

A
0.8
0.6
0.4
0.2
0
100
200
300
400
Time / s
1
2a
3a,b
4a,b
5a
6a,b
5b
2b
7a,b
A
0.8
0.6
0.4
0.2
6.0
6.5
7.0
7.5
8.0
8.5
Time / s
2b
7a,b

FIG. 5b

FIG. 5a

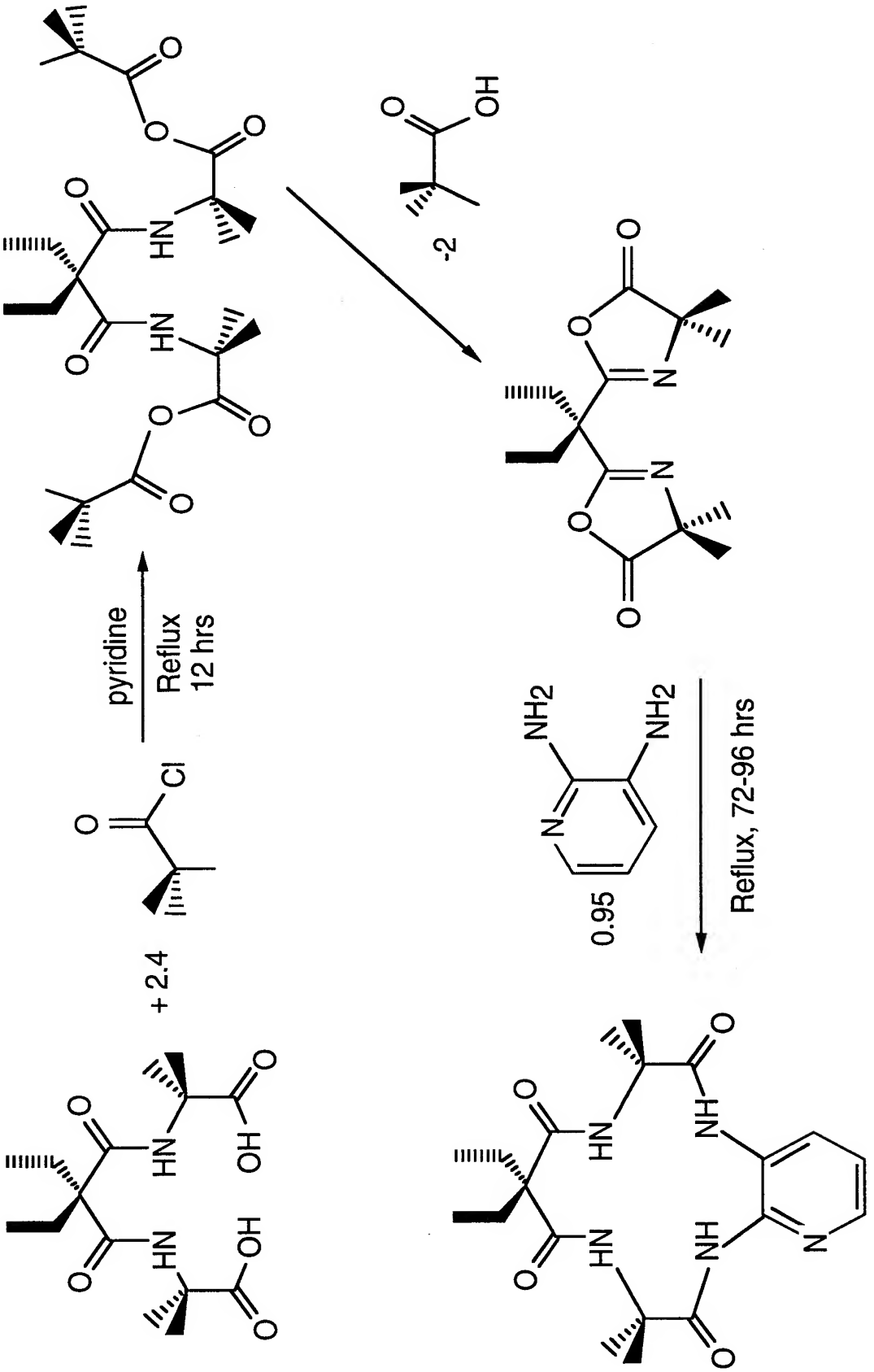


FIG. 6

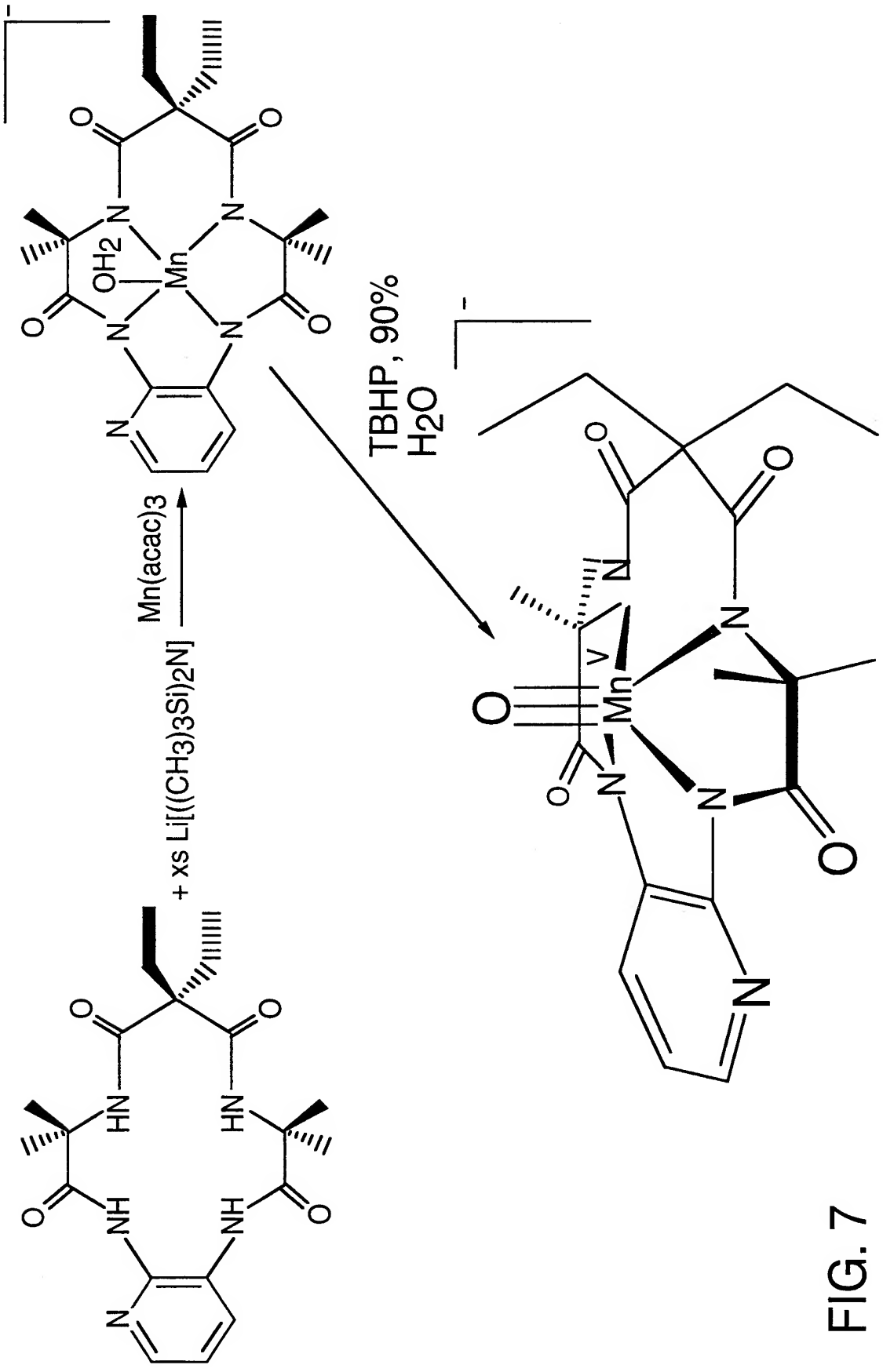


FIG. 7

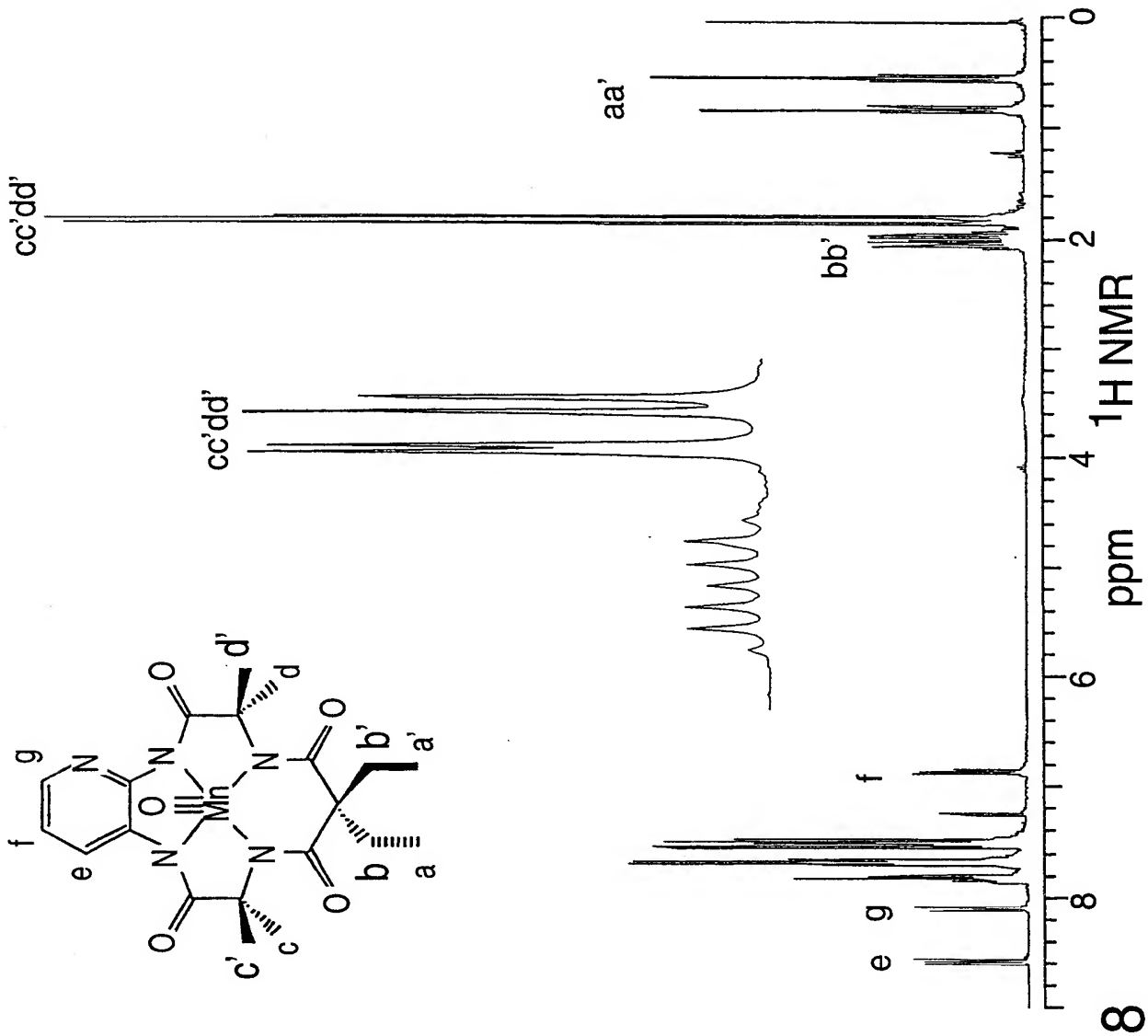


FIG. 8

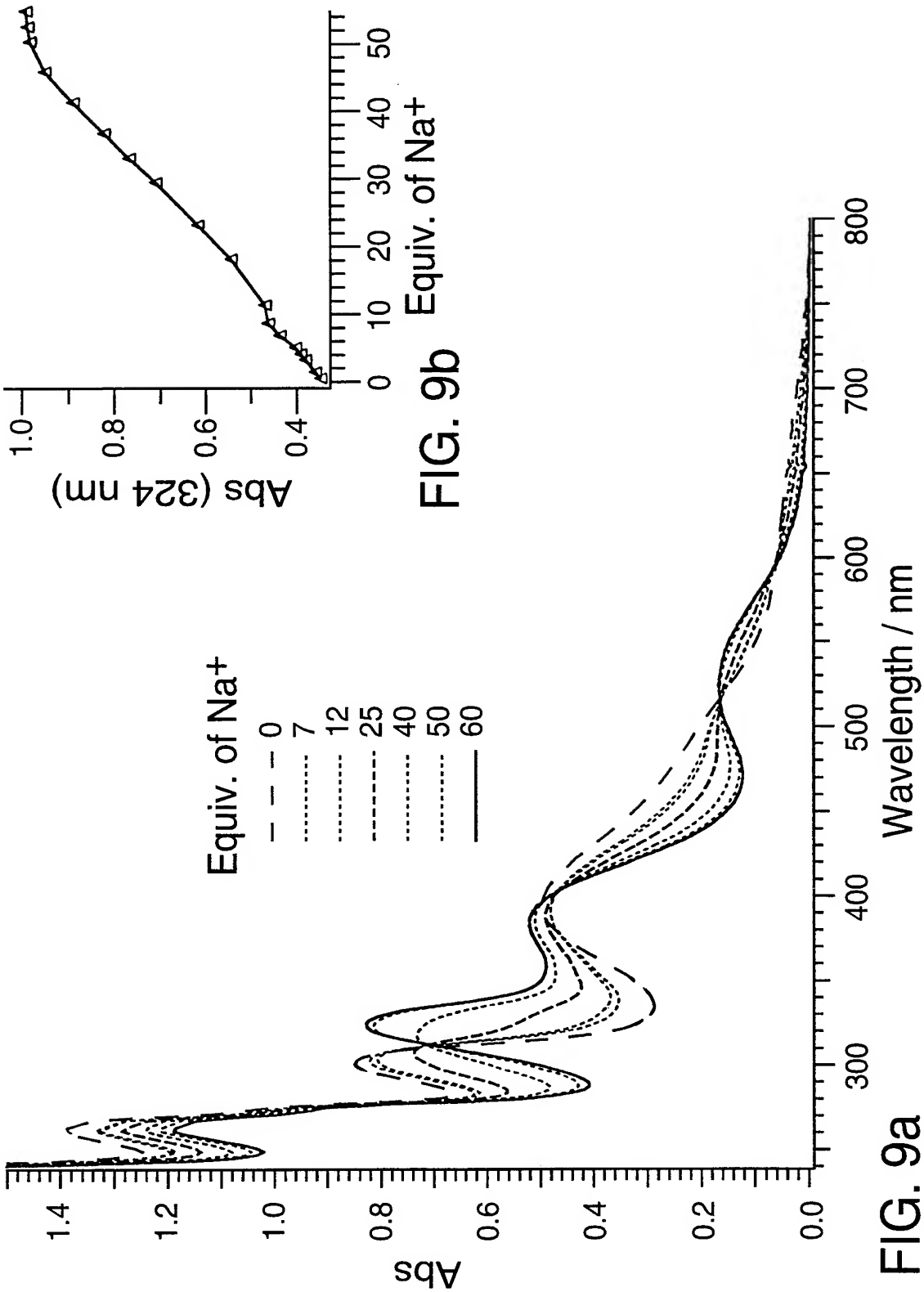
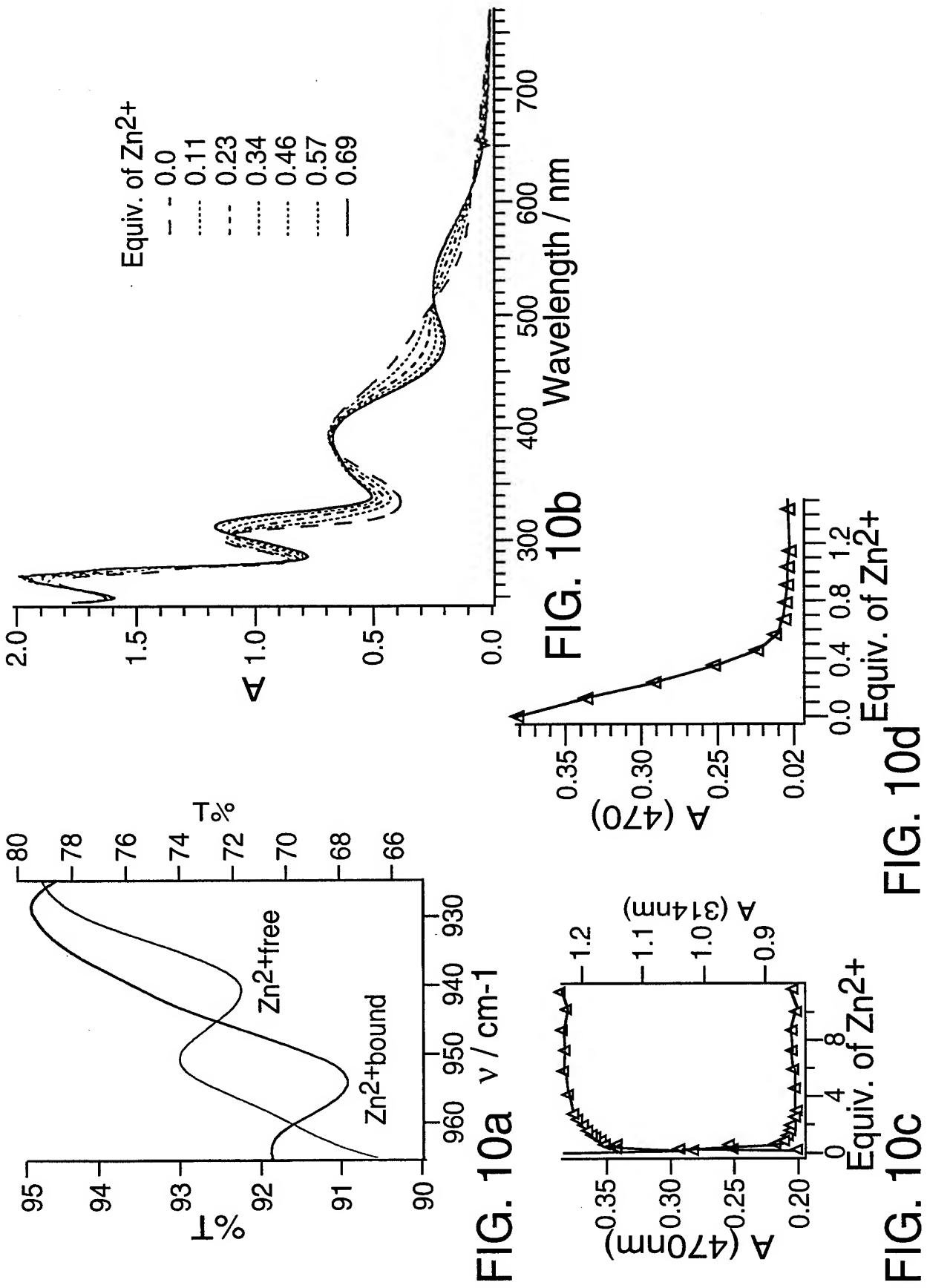

Abs
Wavelength / nm
Equiv. of Na+
0
7
12
25
40
50
60
Abs (324 nm)
Equiv. of Na+

FIG. 9a

FIG. 9b


Equiv. of Zn2+
0.0
0.11
0.23
0.34
0.46
0.57
0.69
A
Wavelength / nm
FIG. 10b
A (470)
Equiv. of Zn2+
FIG. 10d
T%
Zn2+free
Zn2+bound
ν / cm-1
FIG. 10a
A (470nm)
A (314nm)
Equiv. of Zn2+
FIG. 10c

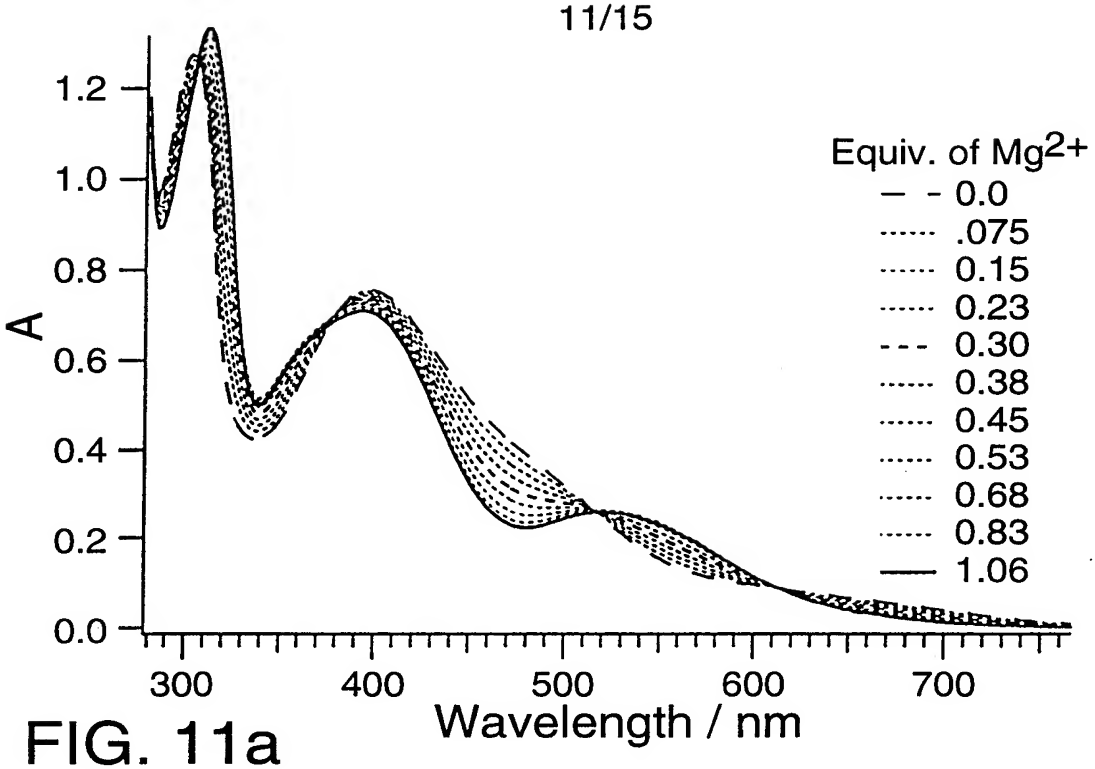


FIG. 11a

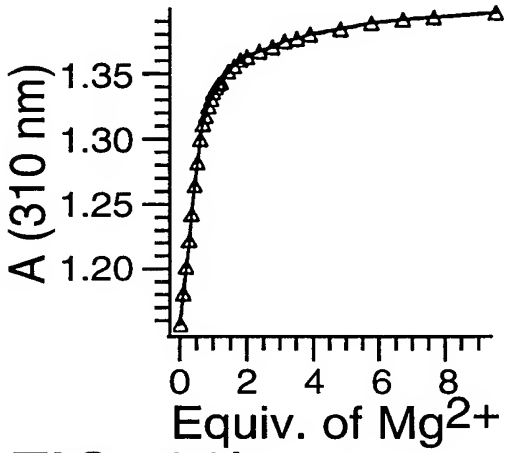


FIG. 11b

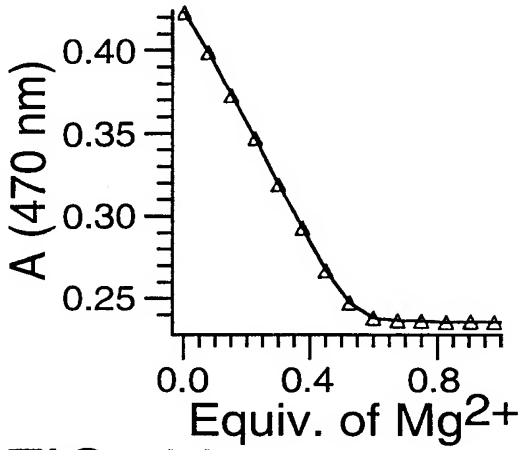


FIG. 11c

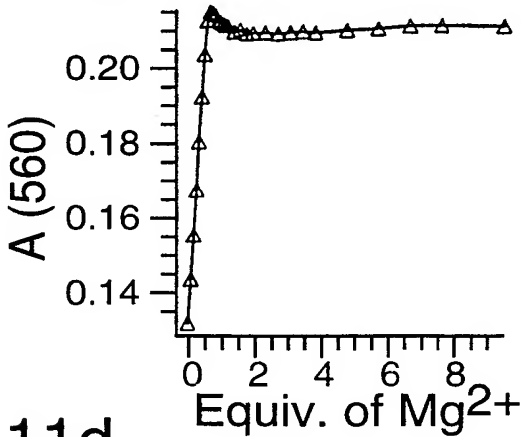


FIG. 11d

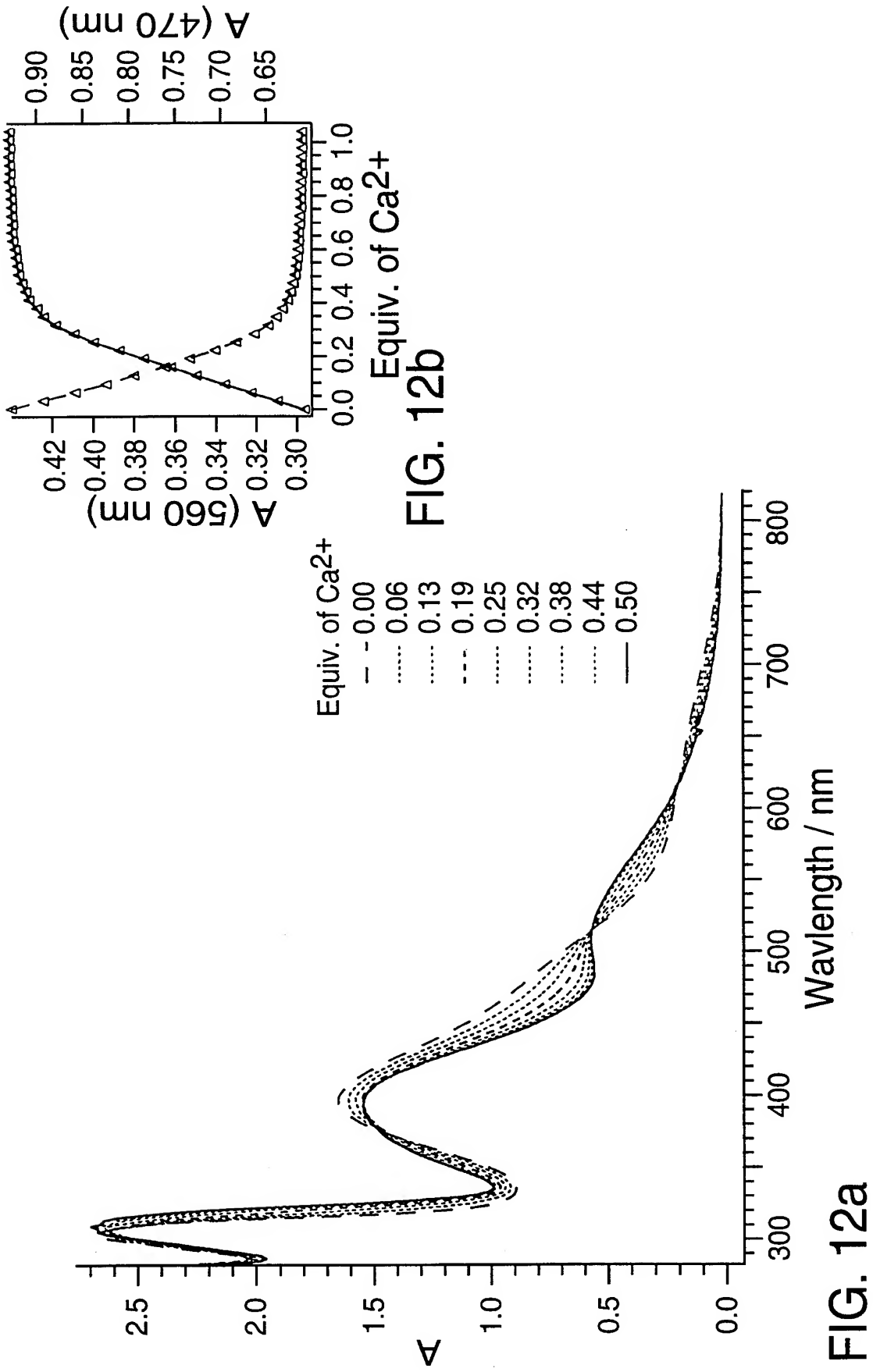


FIG. 12b

FIG. 12a

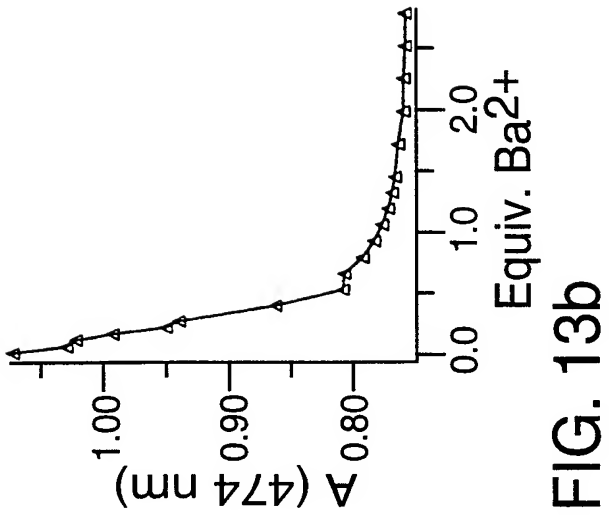


FIG. 13b

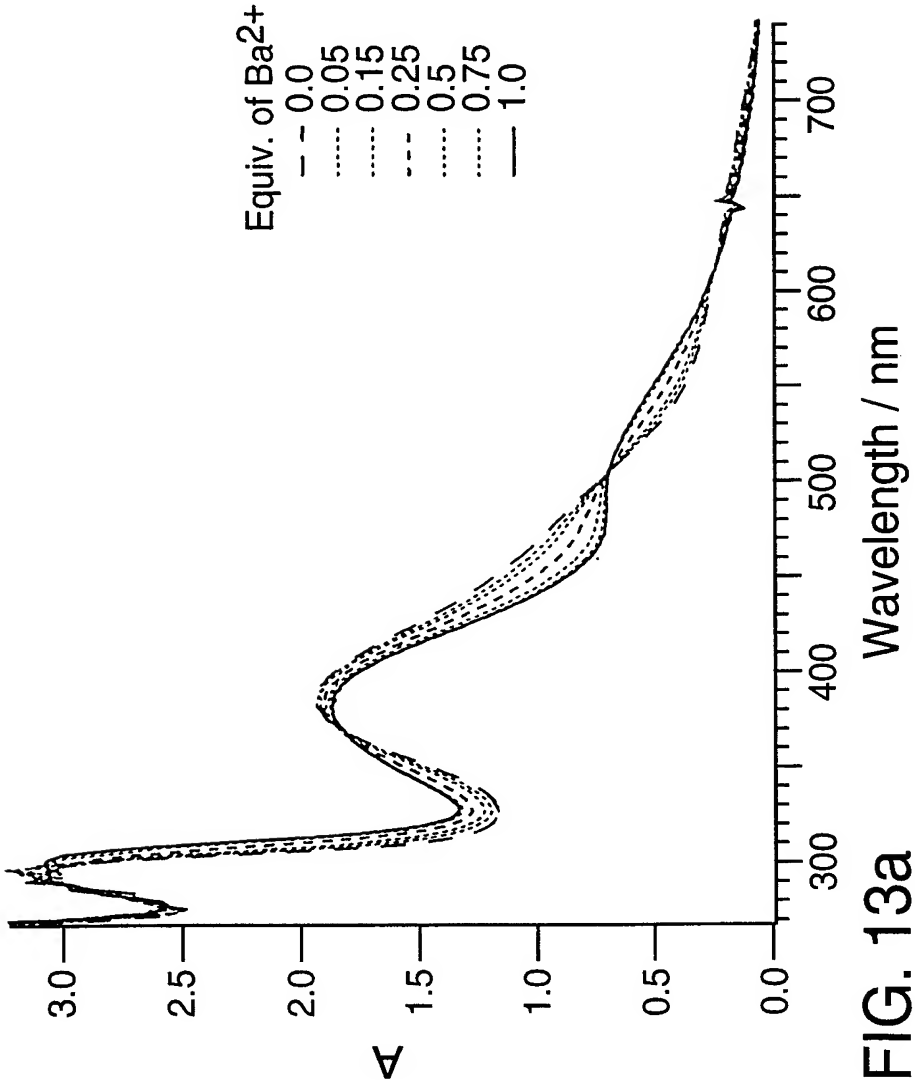


FIG. 13a

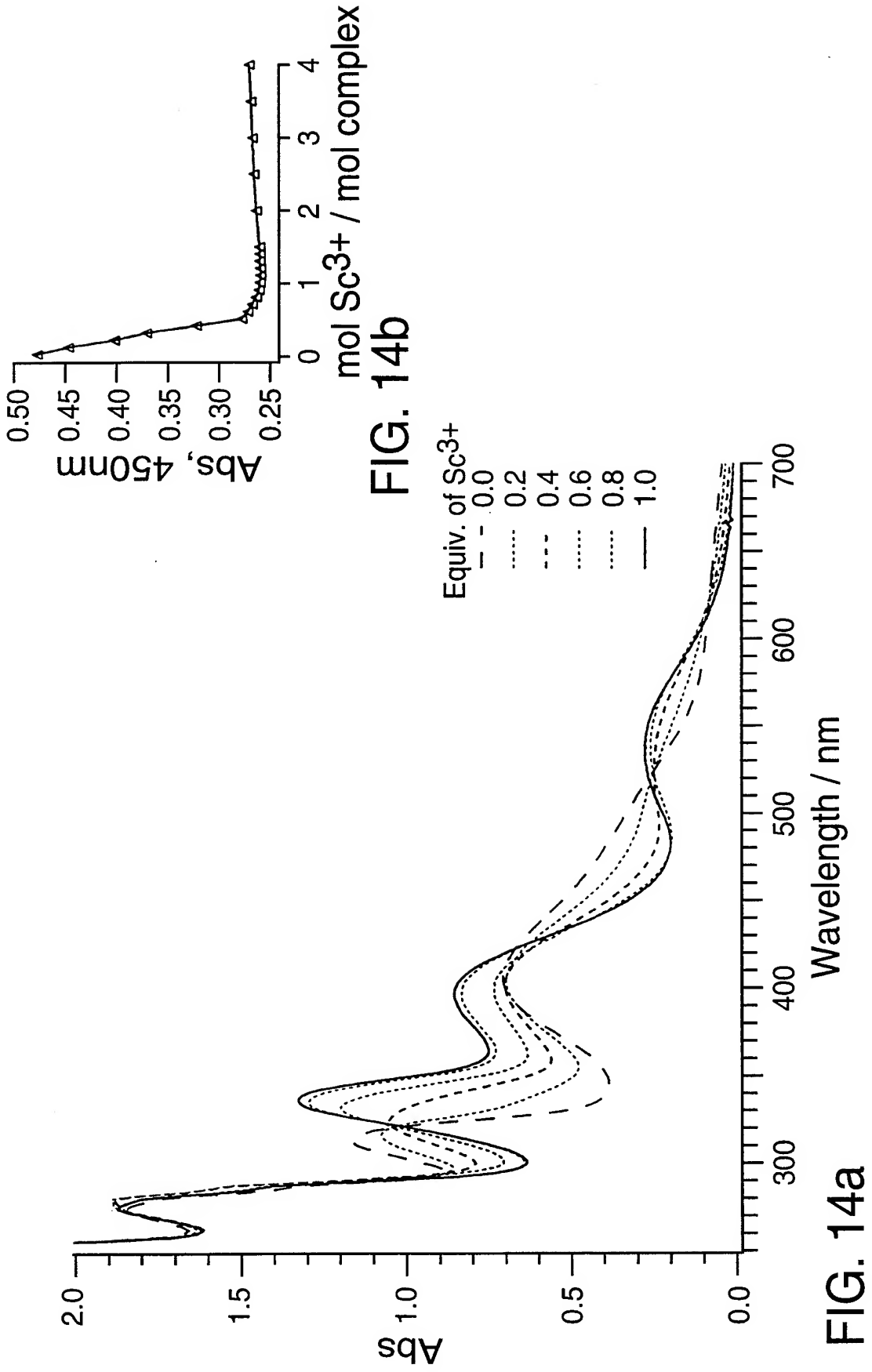


FIG. 14a

FIG. 14b

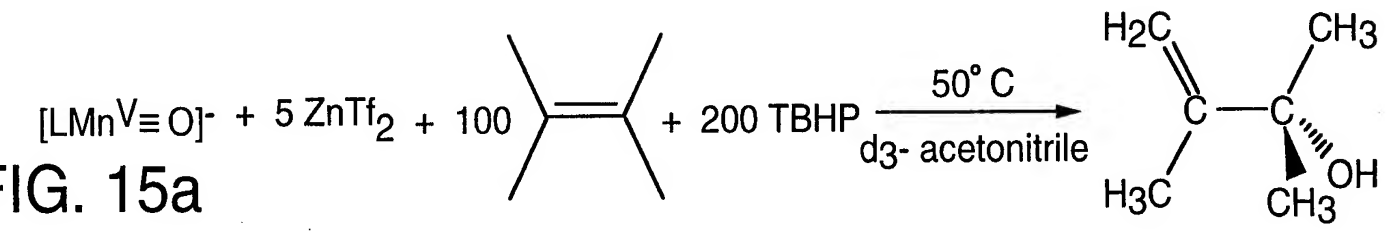


FIG. 15a

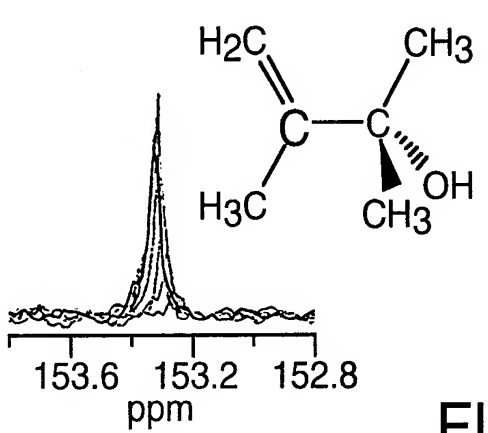


FIG. 15b

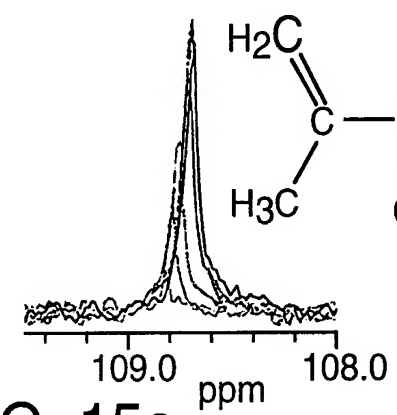


FIG. 15c

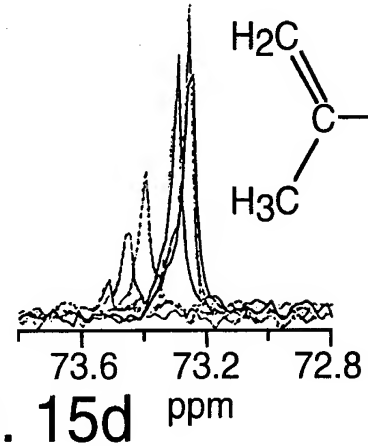


FIG. 15d

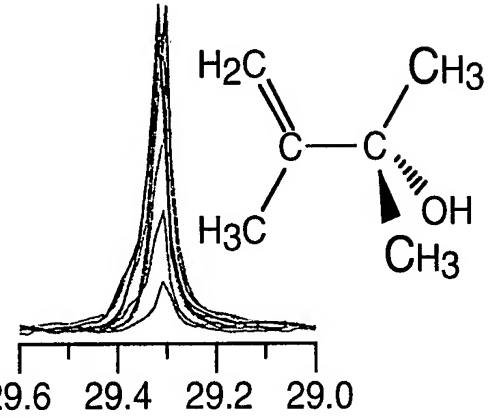


FIG. 15e

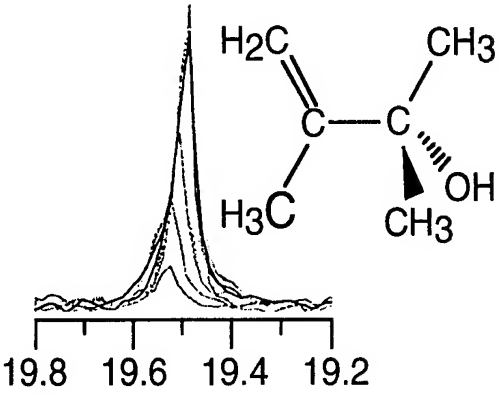


FIG. 15f

INTERNATIONAL SEARCH REPORT

Ii ational Application No
PCT/US 98/12749

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J31/18 B01J31/22 C07B53/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COLLINS T J: "DESIGNING LIGANDS FOR OXIDIZING COMPLEXES" ACCOUNTS OF CHEMICAL RESEARCH, vol. 27, 1994, pages 279-285, XP002048603 cited in the application	
T	WO 98 03263 A (UNIV CARNEGIE MELLON) 29 January 1998	
A	US 4 758 682 A (COLLINS TERRENCE J ET AL) 19 July 1988	
A	WO 96 28402 A (HARVARD COLLEGE) 19 September 1996	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 1998	29/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schwaller, J-M

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

I. ational Application No
PCT/US 98/12749

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803263 A	29-01-1998	AU 4043697 A	10-02-1998
US 4758682 A	19-07-1988	US 4577042 A	18-03-1986
WO 9628402 A	19-09-1996	US 5665890 A	09-09-1997
		AU 5363996 A	02-10-1996
		CA 2213007 A	19-09-1996
		EP 0817765 A	14-01-1998
		NO 974234 A	13-11-1997